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American Heart Journal

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Original Communications

THE SUPERIOR VENA CAVAL SYNDROME; REPORT OF THIRTY-FIVE CASES

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INTRODUCTION

THE syndrome of obstruction of the superior vena cava is produced by any condition which interferes with the flow of blood through that vessel without a corresponding interference with blood flow through the inferior vena cava. Renewed interest in this syndrome has been stimulated by phlebography and measurements of the venous pressure. These techniques have made possible the recognition of the syndrome in cases in which it might otherwise have been undetected. It is only by means of these procedures that the diagnosis can be confirmed during life.

Ehrlich, Ballon, and Graham[1] reviewed the literature on the subject of obstruction of the superior vena cava and collected 309 cases up to 1933. They considered as authoritative the prior reports of Fischer[2] and Brown[3] on the etiology of the condition. Apparently, from a review of the literature approximately 35 per cent of the cases are caused by aortic aneurysm, 50 per cent by thoracic neoplasms (primary or metastatic), and the remaining 15 per cent by a variety of rare causes, some undetermined.

The only etiological factor for the superior vena caval syndrome not included in the reviews previously mentioned is communication between an aortic aneurysm and the superior vena cava. In a review of the literature, Armstrong, Coggin, and Hendrickson[4] collected 100 cases of this type of fistula, including two of their own. The association of this condition with the superior vena caval syndrome was not emphasized, but since we have found all of the manifestations of the syndrome in two cases of this condition, it is probable that the syndrome is frequently, if not always, an associated feature. There have been seven more cases reported[5-11] since their review.

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We are presenting 35 cases of the superior vena caval syndrome personally observed at the Gallinger Municipal Hospital and the Georgetown University Hospital. Cases of constrictive pericarditis, in some of which there has been an associated constriction of the superior vena cava, have not been included. Cases of mediastinal emphysema, a rare cause of compression of the superior vena cava, have not been studied by us from the standpoint of the superior vena caval syndrome. Probably when this disorder is extreme both venae cavae are similarly affected.

ANALYSIS OF THIRTY-FIVE CASES

Etiology.—The etiological factors have been classified in Table I. There were 27 cases in which the cause could be verified and eight cases in which it was uncertain. Of the verified lesions, 12 were aneurysms of the ascending aorta of which two had perforated into the superior vena cava, six were bronchogenic carcinomas, five were cases of malignant lymphoma, two were cases of acute lymphocytic leucemia, and there was one case of hypernephroma with mediastinal metastases and one of carcinoma of the ovaries with mediastinal metastases. Thus, all of the cases in which the cause of the superior vena caval syndrome was verified were due either to aneurysm or to a malignant neoplasm. In addition, in four of the eight cases in which the cause of the syndrome was not verified, a mediastinal mass was demonstrated in the roentgenogram of the chest, but its exact nature was not definitely established. In the remaining four cases there was no roentgenographic evidence of a mediastinal tumor and no clinical evidence of the cause of the syndrome.

The ages of the patients ranged from 15 to 68 years in the 35 cases. Twenty-five were more than 40 years old. Thirty of the 35 patients were males. The sex incidence is explicable on the basis of the predominance of aneurysm, bronchogenic carcinoma, and malignant lymphoma in males. The age distribution is accounted for by the fact that aortic aneurysm and bronchogenic carcinoma occur usually after the age of 40. As far as we can determine, race is of

TABLE I. ETIOLOGY OF SUPERIOR VENA CAVAL SYNDROME IN THIRTY-FIVE CASES

DIAGNOSIS	METHOD OF VERIFICATION			TOTAL
	AUTOPSY	BIOPSY	CLINICAL	
VERIFIED CASES				
Aortic aneurysm	2	0	8	10
Aortic aneurysm with perforation into superior vena cava	2	0	0	2
Bronchogenic carcinoma	3	2	1	6
Hypernephroma with mediastinal metastases	1	0	0	1
Carcinoma of ovaries with mediastinal metastases	1	0	0	1
Acute lymphocytic leucemia	1	1	0	2
Malignant lymphoma	0	5	0	5
Totals	10	8	9	27
UNVERIFIED CASES				
Mediastinal mass (x-ray), nature unknown				4
Superior vena caval obstruction without x-ray or other evidence of cause				4
Total				8

no etiological significance. In our cases, 12 were white persons and 23 were Negroes, but this ratio corresponds approximately to the hospital census for these two races.

Symptomatology.—The incidence of symptoms in general in the 35 cases of superior vena caval syndrome is shown in Table II. In a consideration of the symptoms in patients with this syndrome, a distinction must be made between symptoms which are a part of the syndrome and those which are not part of it but are due to the underlying causative disease.

There were 28 cases in which dilated veins, indicative of obstruction of the superior vena cava, were noted. In eight cases, only the cervical veins were engorged; in eight cases the veins of the neck and chest were dilated; in eight cases engorgement involved the veins of the neck, chest, and arms; and in four cases the veins of the abdomen were dilated in addition to those of the neck, chest, and arms. In two cases of this last group the veins of the posterior thoracic wall were also dilated.

There were 27 cases in which dyspnea was present, and in 10 it was the initial symptom. In 13 of the 27 cases the dyspnea seemed clearly to be related to the obstruction of the superior vena cava, while in the remaining 14 cases the underlying disease was of such character as to account for dyspnea. In these cases it was impossible to appraise the part played by the superior vena caval syndrome as a contributing factor. However, it is noteworthy that when other manifestations of superior vena caval obstruction had appeared, there was no significant change in the degree of dyspnea already present.

There were 25 cases in which a cough was present, and in six cases it was the initial symptom. However, in only two of the 25 cases could the cough possibly be attributed to the obstruction of the superior vena cava. Both of these were patients in whom there was no evidence of the cause for the syndrome. In the other 19 cases the cough was due to the underlying disease. The cough was described as "brassy" in four cases, in all of which the diagnosis was aneurysm.

TABLE II. SYMPTOMATOLOGY OF SUPERIOR VENA CAVAL SYNDROME IN THIRTY-FIVE CASES

SYMPTOM	NUMBER OF CASES	NUMBER OF CASES IN WHICH SYMPTOM INDICATED SUPERIOR VENA CAVAL SYNDROME
Dilated veins of superior vena caval system	28	28
Dyspnea	27	13
Cough	25	2
Edema in distribution of superior vena cava	20	20
Loss of weight	16	0
Pleural effusion	8	2
Pain in chest	11	0
Cyanosis	9	5
Hemoptysis	8	0
Hoarseness	8	1
Dysphagia	3	1
Drowsiness or stupor	2	2
Jacksonian convulsion	1	0
Generalized convulsion	1	1
Pain in face	1	1

In 20 cases there was edema in part or all of that portion of the body drained by the superior vena cava. In all cases this sign was indicative of obstruction of the superior vena cava, and in 12 cases it was the first evidence of the syndrome. The face was edematous in all but one of the 20 cases; in this case, only the neck was swollen. In nine cases there was swelling of one or both arms in association with edema elsewhere. The thoracic wall was edematous in four cases, in two of which the edema was restricted to the right side.

Loss of weight to an impressive degree was noted in 16 cases, and in one case it was the initial symptom. In 13 of these cases a neoplasm was present. In none of the cases was loss of weight directly related to the superior vena caval syndrome.

Pleural effusion was demonstrated in eight of the 35 cases. In four it involved the right side, in three the left, and in one case it was bilateral. In two cases obstruction of the superior vena cava was responsible for the effusion, and in both it was right-sided. In the remaining five cases of unilateral pleural effusion it is possible that the obstruction of the superior vena cava was the cause, but in every instance the disease responsible for the obstruction was neoplastic and therefore was sufficient cause in itself for pleural effusion. The single case of bilateral effusion resulted from obstruction of the thoracic duct by metastatic carcinoma which produced chylothorax.

In 11 cases there was pain in the chest, and in six of these it was an initial symptom. The chest pain had no relation to the superior vena caval syndrome in any case.

Cyanosis was observed in nine of the 35 cases. In five the superior vena caval obstruction was the basis for the sign. Two of the latter group were cases of aortic aneurysm with perforation into the superior vena cava, one was a case of uncomplicated aortic aneurysm, and in two the cause of superior vena caval obstruction was unknown. In four of the group with cyanosis the syndrome developed acutely and was severe. The cyanosis in these was limited to the part of the body drained by the superior vena cava and had a distinctive reddish cast. In four cases the superior vena caval obstruction was not the sole cause for the cyanosis. Three were instances of bronchogenic carcinoma; one with almost complete tracheal obstruction, one with atelectasis, and one with massive pleural effusion. The fourth patient had massive chylothorax due to obstruction of the thoracic duct by metastatic carcinoma.

There were eight cases in which hemoptysis occurred, and in all of these a malignant intrathoracic neoplasm accounted for the symptom. Five of them were cases of bronchogenic carcinoma.

Hoarseness was noted in eight cases, in all of which it was apparently due to involvement of the recurrent laryngeal nerve by a mediastinal mass. It is possible that in one patient at least the superior vena caval obstruction may have contributed to the hoarseness by the edema of the larynx which it caused.

Dysphagia was present in three cases, in two of which an aneurysm compressed the esophagus. The remaining case was one of severe and sudden superior vena caval obstruction of unknown cause. In this patient intense edema of the pharynx explained the difficulty in swallowing.

Drowsiness and stupor were noted in two cases. In both there was acute severe obstruction of the superior vena cava.

In one patient Jacksonian convulsions were present and were ascribed to cerebral metastases from a bronchogenic carcinoma.

In a case of superior vena caval obstruction due to malignant lymphoma, the patient had generalized convulsions whenever he was recumbent. In this position the intracranial pressure is greatly increased when the superior vena cava is obstructed, and this fact accounts for the relation of the convulsions to posture.

In a patient with aortic aneurysm with perforation into the superior vena cava, pain in the face was associated as an initial complaint with the intense facial edema.

In summary, a glance at Table II indicates that, while a wide variety of symptoms is found in the superior vena caval syndrome, actually only a few are directly indicative of the syndrome. Thus, dilated veins and edema in the distribution of the superior vena cava denoted obstruction of this vessel in all instances in which these signs were present. Other manifestations such as dyspnea, cough, pleural effusion, cyanosis, hoarseness, and dysphagia, were sometimes part of the syndrome but were more frequently ascribable to the disease which caused the syndrome. Drowsiness, generalized convulsions, and pain in the face were infrequent symptoms. In the 35 cases there were other symptoms which we have omitted from tabulation because they obviously had no relationship to obstruction of the superior vena cava.

Venous Pressure Measurements.—The venous pressure was measured in an antecubital vein in 34 of the 35 cases. The technique for this measurement was a modification of the direct method and is described elsewhere in detail.[12] In this procedure the patient is required to rest quietly for at least thirty minutes beforehand. The measurement is obtained with the patient supine, and the arm abducted at an angle of 45 degrees from the chest, with the surface of the antecubital fossa at or just below the zero level of the venous pressure manometer, which is referred to a point 10 cm. from the skin of the patient's back. By this method the normal range of the venous pressure is from 50 to 150 mm. of saline. The apparatus includes a three-way stopcock which provides a means for conveniently measuring the circulation time with the same venipuncture.

Fig. 1 shows the range of the initial venous pressure measurements in the 34 cases in which they were obtained. It is apparent from this chart that the venous pressure was 300 mm. of saline or above in 20 of the 34 cases and was 400 mm. or more in 12. In six cases the venous pressure was below 200 mm. and might ordinarily have been accepted as normal. However, in each of these the pressure in the femoral vein was very much lower, indicating that there was obstruction of the superior vena cava.

The venous pressure was measured in both arms in 32 cases, the second reading being made immediately after the first. Normally, the venous pressure does not differ in the two arms by more than 10 millimeters. In nine of the 32 patients a significant difference was noted. The differences ranged from 25 to 87

millimeters. This variation in the venous pressure in the two arms indicates that there is obstruction, on the side in which the venous pressure is higher, in one of the tributaries of the superior vena caval system (usually the innominate vein), in addition to obstruction of the vena cava itself. In six of the patients the higher reading was in the left arm, and five of these were cases of aneurysm. The arch of the aorta also is involved frequently in aneurysm of the ascending limb. The tendency for the venous pressure to be higher in the left arm in cases of aortic aneurysm has been ascribed to the close relationship of the left innominate vein to the arch of the aorta.[13] In two of the cases in which the venous pressure was higher in the right arm there was a malignant neoplasm, and in one there was a saccular aneurysm of the ascending aorta.

In 18 of the 34 cases in which the venous pressure was measured, the "exercise test"[14] was performed. This test consists in having the patient open and clench the hand forcefully and repeatedly for one minute while the venous pressure is being measured on that side. It is important that the patient use only the muscles of his forearm. Normally, and in patients with elevation of the venous pressure due to heart failure this exercise causes little or no change in the venous pressure, and in no instance is there a rise exceeding 10 millimeters. On the other hand, in cases of obstruction in any part of the venous system of which the arm veins are tributaries, there will be a prompt rise of 10 mm. or more. Exercise causes an increase in blood flow into the extremity and therefore an increase in venous return from that extremity. When the venous system is patent, this has little or no effect on the venous pressure. However, when the venous system is obstructed, an increase in venous return cannot be accomplished without a rise in venous pressure. Usually, the response to the "exercise test" is greatest when the venous obstruction is complete and the collateral circulation is relatively undeveloped. In obstruction of the superior vena cava a positive response to the "exercise test" is to be expected in both upper extremities. In the 18 cases the resulting increments in venous pressure during the test ranged from 20 to 200 mm. of saline and are shown graphically in Fig. 1.

When the venous pressure is measured by the direct method (the column of saline in the measuring tube normally oscillates with respiration, falling slightly on inspiration and rising slightly on expiration. In two of our cases in which close attention was paid to the respiratory oscillation of the liquid in the manometer, a paradoxical effect was observed. In other words, the column rose with inspiration and fell with expiration. In both instances the obstruction of the superior vena cava was complete and was below the point of entrance of the azygos vein. In one case the spinal fluid pressure was measured, and a similar paradoxical effect from respiration was noted. These observations confirm the report by Hitzig[15] that in superior vena caval obstruction in which the azygos vein is also obstructed, the effect of respiration on the venous pressure and spinal fluid pressure is the opposite of what is found normally. This type of paradoxical oscillation is the normal finding when the venous pressure is measured in the inferior vena caval system and is therefore evidence that the

principal collateral channels enter the inferior vena cava. Another way of demonstrating that the level of obstruction of the superior vena cava is below the azygos vein is by means of encircling the lower part of the chest with a constricting band.[15] This procedure blocks the superficial veins which carry blood to the inferior vena caval system. Consequently the venous pressure rises in the arms. When the obstruction is above the azygos vein the superficial thoracic veins drain mainly into the azygos, so that the constricting band around the thorax causes no rise in venous pressure in the arm.

In most of our cases the venous pressure was measured repeatedly during the patient's hospital stay. In nine there was a marked lowering of the venous pressure, ranging from 65 to 305 millimeters. The reasons for this decrease varied and were as follows: (1) development of collateral circulation (four cases), (2) shrinkage of a mediastinal tumor with x-ray therapy (four cases), and (3) relief of complicating heart failure (one case).

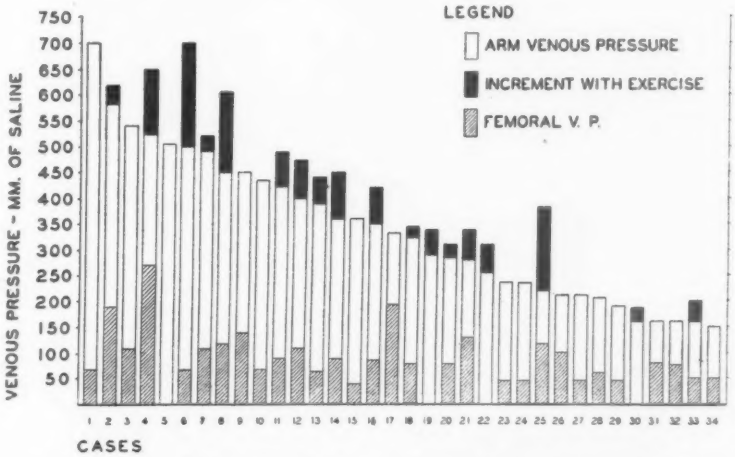

Fig. 1.—Graphic illustration of the heights of the venous pressures in the arms, their increments with exercise of the hand, and the femoral venous pressures in cases in which two or three of these measurements were made. Where a black block is not shown the exercise test was not performed.

In order to demonstrate that the venous pressure is elevated mainly in the superior vena caval system, measurement of the pressure in the femoral vein is desirable. This measurement was made at the same time that the antecubital venous pressure was recorded in 30 of our patients, using the same reference point for the zero level of the manometer. The results are shown in Fig. 1. The femoral venous pressure was normal (below 150 mm.) in 27 cases and higher than 150 mm., but nevertheless considerably lower than the venous pressure, in the arms in three. In one of this latter group, there was a communication between an aortic aneurysm and the superior vena cava. Presumably there was general elevation of the venous pressure in this case because of interference with entrance of blood into the right auricle due to the arteriovenous fistula. In another case the femoral venous pressure was higher than normal because the

measurement was made with the patient in a semisitting position because she was too dyspneic to lie flat. Another reason for the elevated pressure in the femoral vein was encroachment on the right auricle by the mediastinal mass. In the third case a hypernephroma invaded the inferior vena cava, causing the femoral venous pressure to be higher than normal. The superior vena cava was involved because of metastasis to the mediastinal lymph nodes.

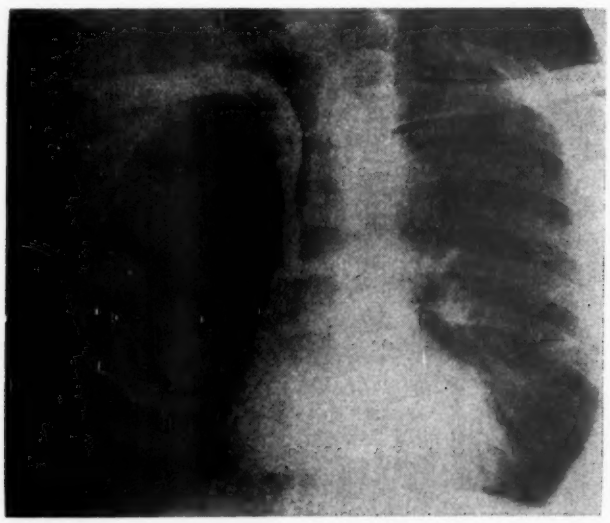

Fig. 2.—Normal phlebogram of superior vena cava after injection of Diodrast into right antecubital vein.

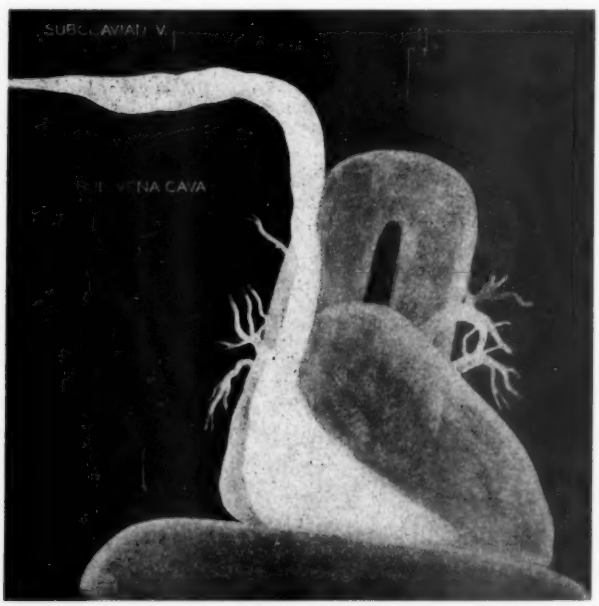

Fig. 3.—Partial drawing of roentgenogram shown in Fig. 1, showing normal contour of vessels from axillary vein to right auricle with contrast medium in the latter.

Circulation Time Measurements.—The arm-to-tongue circulation time was measured in 20 cases by using 6 c.c. of 10 per cent magnesium sulfate or 5 c.c. of 20 per cent calcium gluconate. The measurement was made in each instance just before the venous pressure was recorded so that the same venipuncture served for both tests. The circulation time with this technique normally varies from 9 to 16 seconds. In superior vena caval obstruction it seems logical to expect that the circulation time should be prolonged because of the circuitous route which the blood must take through the collateral pathways. However, in four of the 20 cases the result was normal although the venous pressure was quite high (220 mm., 260 mm., 505 mm., and 540 mm.). Furthermore, in an

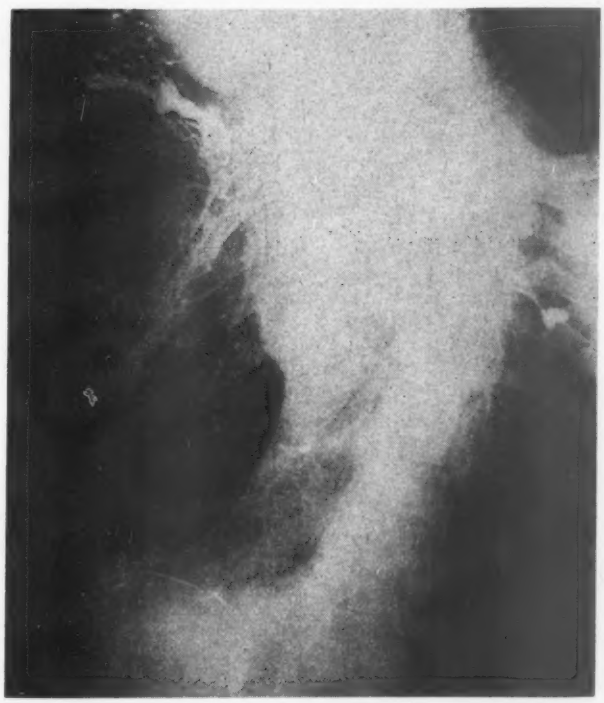

Fig. 4.—Left oblique exposure of phlebogram with Diodrast injected into right antecubital vein in case of mediastinal lymphoma. Much detail is lost in reproduction but this is shown in drawing of roentgenogram in Fig. 5.

additional eight cases the circulation time was from 16 to 26 seconds with the venous pressure ranging from 290 to 525 millimeters. This is an obvious disproportion in the light of experience with circulation tests in heart failure.[12] Therefore, in the majority of our cases in which both the venous pressure and the circulation time were measured, the circulation time was disproportionately low. In the remaining eight cases the circulation time was prolonged in proportion to the height of the venous pressure.

Phlebography.—Phlebograms were made in 13 cases using Diodrast or Thorotrast. Injections were made into a suitable vein in one arm, or simul-

taneously into veins of both arms, or into the external jugular vein. Best results were obtained with a large bore needle inserted into the external jugular vein for the purpose of rapid injection of 20 to 30 c.c. of 70 per cent Diodrast.

Fig. 2 is a roentgenogram made after injection of Diodrast into the right antecubital vein, showing the normal appearance of the right subclavian vein, right innominate vein, superior vena cava, and right auricle. Fig. 3 is a carefully executed drawing of this roentgenogram. In three cases the phlebogram showed the narrowing of the superior vena cava (two cases) or its point of obstruction (one case), as shown in Figs. 4, 5, 6, 7, and 8. In another case injection of the left jugular vein showed the Diodrast to fill the left innominate vein

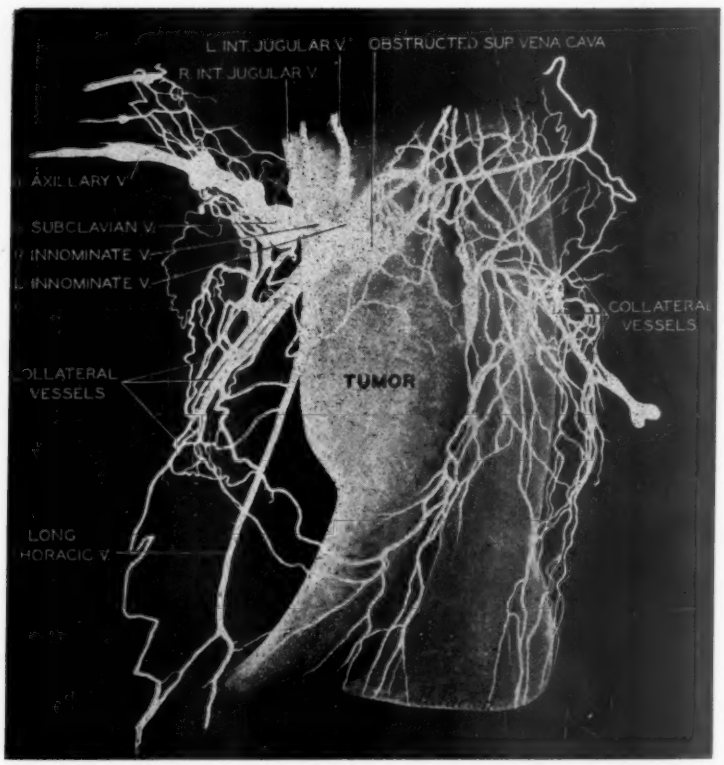

Fig. 5.—Drawing made from roentgenogram shown in Fig. 4, indicating point of obstruction of superior vena cava near its origin and illustrating the extensive collateral network.

and end at its junction with the superior vena cava (Figs. 9 and 10). In one case simultaneous injections of both antecubital veins showed the Diodrast only as far as the innominate veins (Figs. 11 and 12). In one case left jugular injection showed the Diodrast to reach only into the middle of the left innominate vein, but there were numerous collaterals in the neck, and the right internal mammary vein was shown very prominently (Fig. 13). A very unusual phlebogram in a case which is summarized later as Case 5 is shown in Figs. 14 and 15) and the extreme development of the collateral circulation in this case is illus-

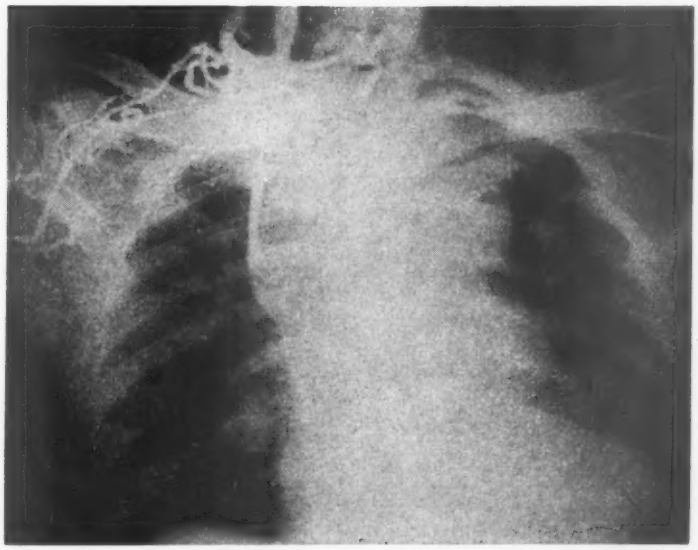

Fig. 6.—Phlebogram after injection of Diodrast into right external jugular vein in case of aneurysm of ascending aorta. Details are shown more clearly in drawing in Fig. 7.

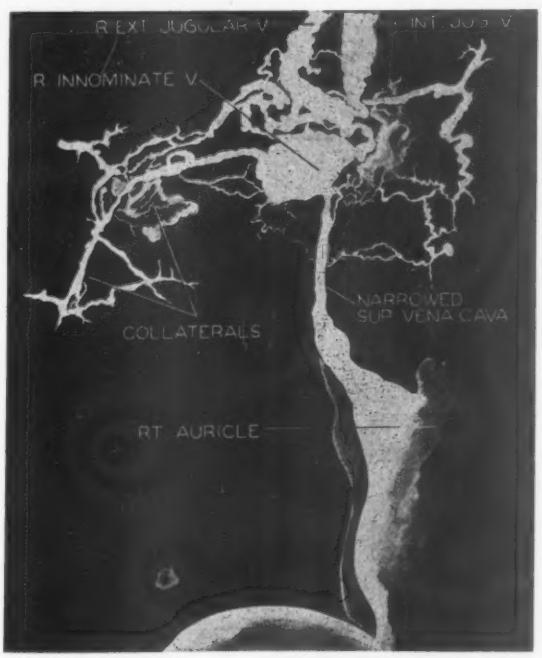

Fig. 7.—Drawing made from phlebogram (Fig. 6) showing reflux of Diodrast into right internal jugular vein, dilatation of right innominate vein, narrowing of superior vena cava, and extensive collateral network in upper part of chest and base of neck.

trated in a phlebogram after injection into the left antecubital vein (Fig. 16). In six other cases, not illustrated, there was evidence of obstruction of the major tributaries of the superior vena cava, although the point of obstruction was not definitely indicated. The evidence consisted of retrograde filling of a major vein out of the path that the injected contrast medium normally would take, such as filling of the homolateral internal jugular after injection into the external jugular vein, venous dilatation, and the presence of a well-developed collateral venous network.

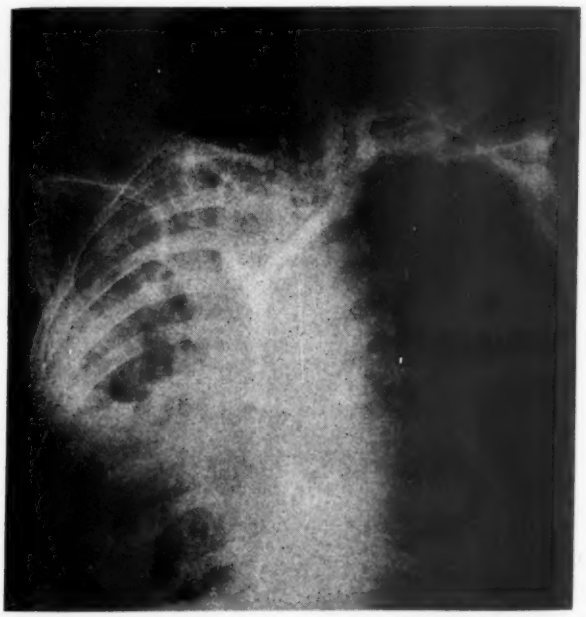

Fig. 8.—Phlebogram after injection of Thorotrast into left antecubital vein in case of bronchogenic carcinoma (Case 3 in series of illustrative cases), showing left subclavian vein, reflux into left internal jugular vein, left innominate vein, reflux into right innominate vein, and narrowed superior vena cava.

Course and Prognosis.—The prognosis in cases of obstruction of the superior vena cava depends mainly on the disease responsible for the obstruction and to some extent on the obstruction itself. The prognosis therefore is usually grave.

There were 17 deaths in our group of 35 patients. In four of these 17 cases the superior vena caval obstruction was the main factor in the death of the patient. In these the obstruction was severe. Two patients had obstruction of the superior vena cava without evident cause which lasted, respectively, two months and eight months. The other two were cases of aortic aneurysm with perforation into the superior vena cava, lasting two weeks and three weeks, respectively.

Twelve of the 35 patients were discharged from the hospital unimproved, five were discharged as improved, and one patient was improved and is still under observation.

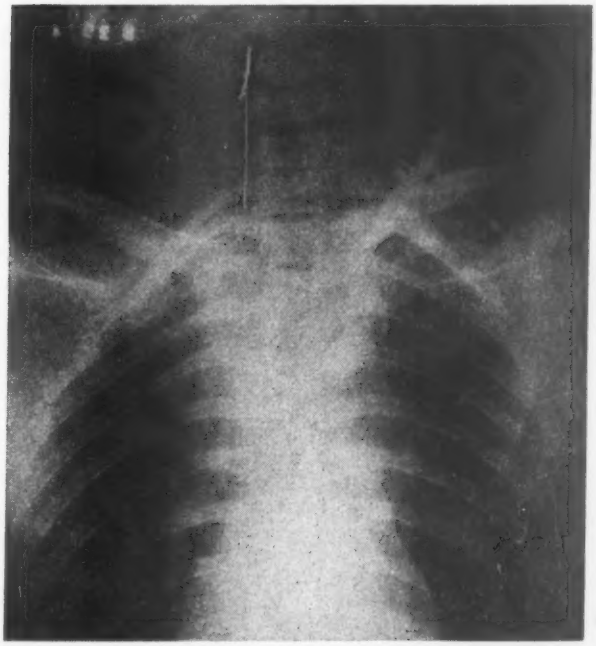

Fig. 9.—Phlebogram made by injecting Diodrast into left external jugular vein in case of malignant lymphoma of mediastinum, showing filling of left innominate vein and collaterals. Details are illustrated in drawing as Fig. 10.

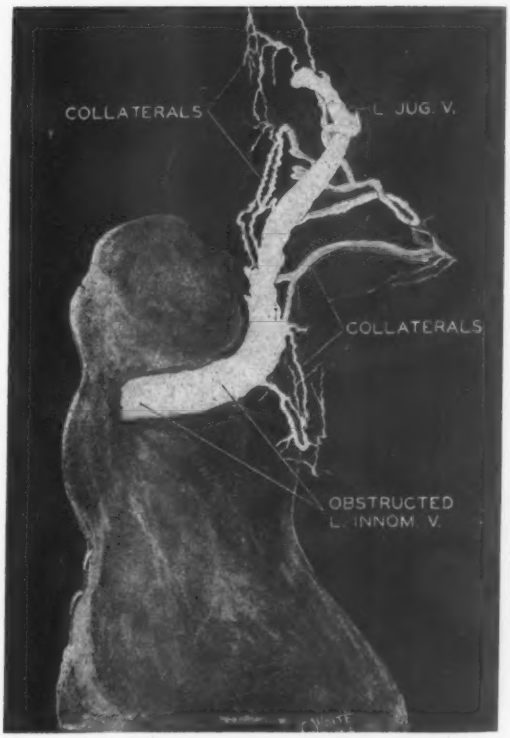

Fig. 10.—Drawing made from phlebogram shown in Fig. 9 with contrast medium ending at point of entrance of innominate vein into superior vena cava.

ILLUSTRATIVE AND SPECIAL CASES

CASE 1.—*Superior Vena Caval Obstruction Without X-Ray or Other Evidence of Cause.*—J. G. (A98689), a 48-year-old Negro, entered the hospital complaining of edema of the face. This had been present for eight days and had been disappearing during the day and reappearing after a night's rest in bed. There were no other significant data in the history.

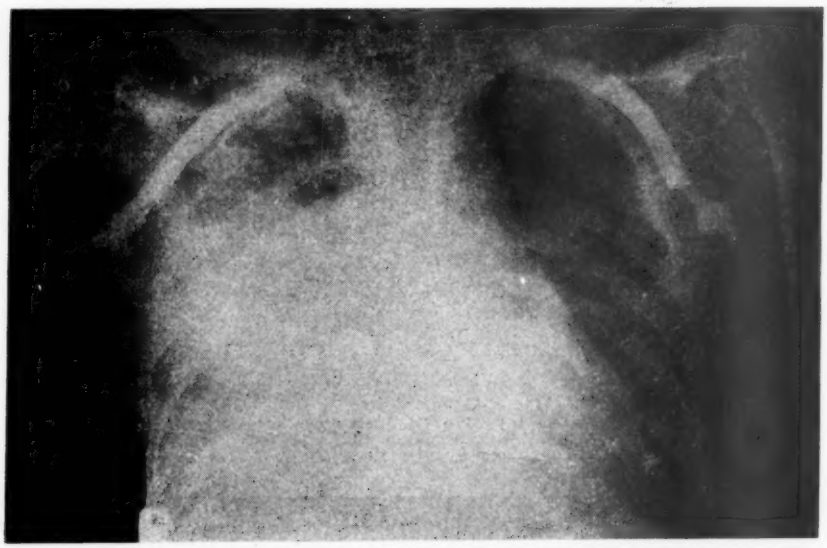

Fig. 11.—Phlebogram made by simultaneous injection of Thorotrast into both antecubital veins in case of bronchogenic carcinoma, showing contrast medium getting no further than innominate veins (see drawing, Fig. 12).

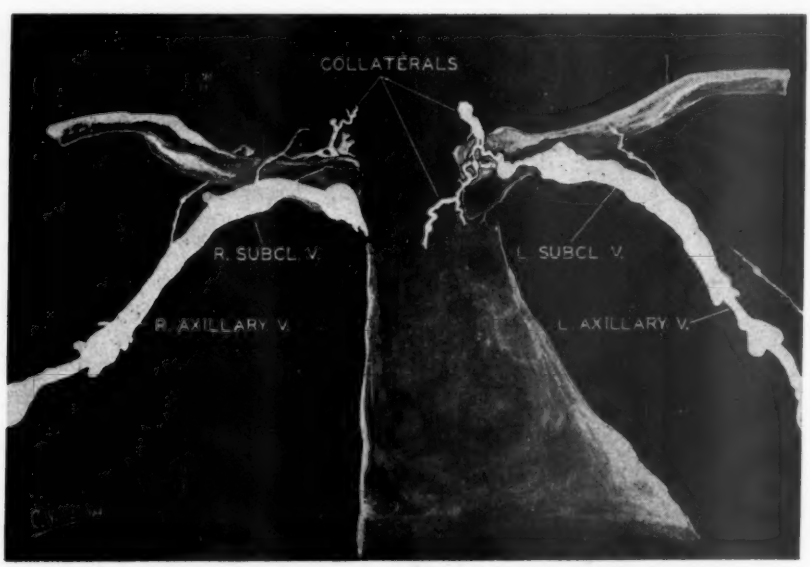

Fig. 12.—Drawing of phlebogram shown as Fig. 11.

On examination, the face was found to be moderately edematous and there was moderate cyanosis of the fingernails. The veins of the neck, arms, and upper part of the chest were distended. The venous pressure in the right arm was 500 mm. of saline, with a rise to 590 mm. after exercise of the hand for one minute. The venous pressure measurements were almost identical in the left arm. The femoral venous pressure was 70 millimeters. X-ray examination of the chest disclosed a fusiform shadow in the right superior mediastinum which was interpreted as a dilated superior vena cava. There were calcified lymph nodes on the right side near the lower end of the superior vena cava. A phlebogram was made by injecting Thorotrast simultaneously into veins of both arms. This showed dilatation of both axillary veins, but the remainder of the superior vena caval system was not visualized. Routine laboratory studies were negative except that the blood Kahn test was 4 plus.

During a period of approximately two months of hospitalization the edema of the face disappeared. The venous pressure in the arm at the time of discharge was 330 mm. and rose promptly to 520 on exercise of the hand.

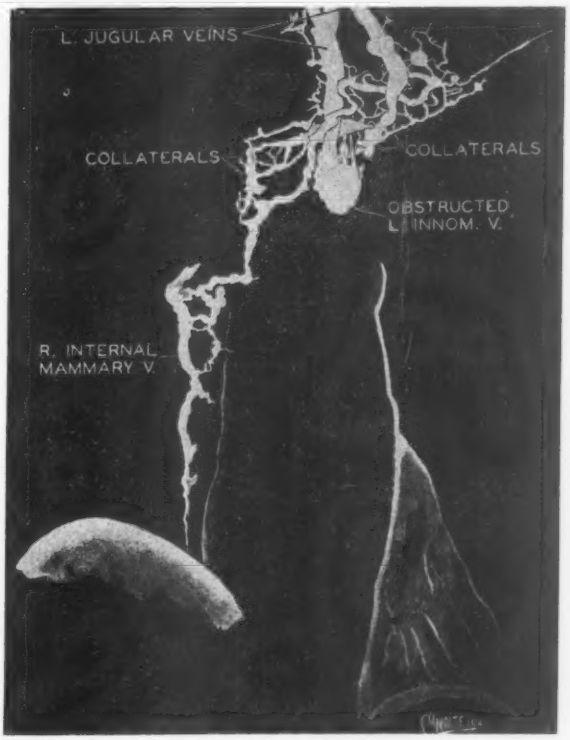

Fig. 13.—Drawing of phlebogram made after injection of Thorotrast into left external jugular vein, showing reflux into internal jugular vein, dilatation and obstruction of left innominate vein, numerous collaterals at base of neck, and right internal mammary vein (case of superior vena caval syndrome without exidence of mediastinal mass).

Comment.—This was a case of obstruction of the superior vena cava without definite evident cause. The presence of calcified hilar lymph nodes suggested that the cause may have been a localized tuberculous mediastinitis. While the patient was under observation, the edema of the face gradually subsided, and the venous pressure in the arm decreased from 500 to 330 millimeters.

CASE 2.—*Incomplete Superior Vena Caval Obstruction Due to Bronchogenic Carcinoma.*—C. W. (B64751), a 35-year-old white man, was admitted to the hospital complaining of cough and thoracic pain of about one year's duration. The cough had been severe and occasionally

productive of blood-streaked sputum. During this period there was loss of strength and weight (7 pounds). Six weeeks before admission the face became swollen.

On examination, moderate edema of the face was found. The veins of the neck and upper part of the chest were distended. Over the upper lobe of the right lung there was dullness, diminished breath sounds, and sonorous râles. The venous pressure in the right arm was 490 mm. of saline. The femoral venous pressure was 110 millimeters. X-ray examination of the chest showed a large mass in the region of the superior mediastinum on the right side and a diffuse opacity of the right upper lobe. Bronchoscopic examination was unsatisfactory.

Deep x-ray therapy to the chest was given repeatedly, and during the ensuing two and one-half months marked improvement resulted. The facial edema disappeared. The mediastinal mass was reduced. The cough was diminished. The venous collateral circulation became less prominent, and the venous pressure came down to 185 millimeters.

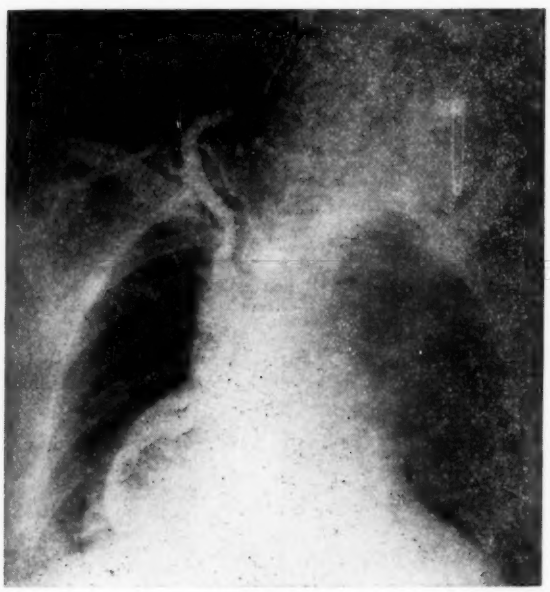

Fig. 14.

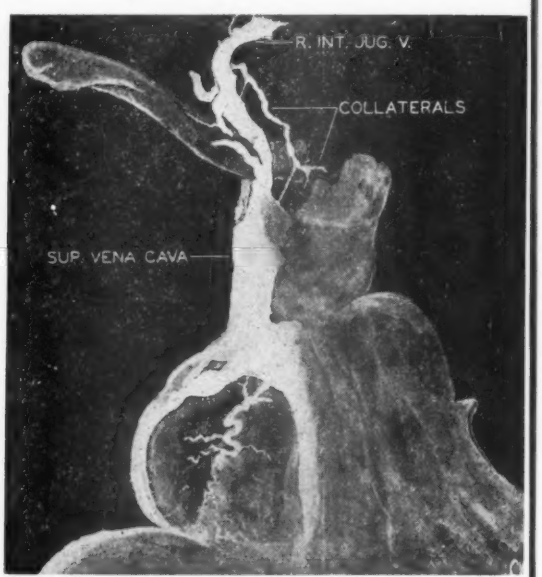

Fig. 15.

Fig. 14.—Phlebogram made after injection of Diodrast into right external jugular vein in Case 5 of series of illustrative cases, showing dilated superior vena cava with contrast medium flowing down along both sides of mediastinal mass (see drawing, Fig. 15).

Fig. 15.—Drawing of phlebogram reproduced in Fig. 14.

The improvement was temporary. Toward the end of the period of observation, the patient suddenly developed severe dyspnea, cough, cyanosis, and stridor. There was no evidence of aggravation of the superior vena caval obstruction. The respiratory embarrassment increased until death about forty-eight hours later.

Necropsy disclosed a carcinoma of the right main bronchus, with extension into and occlusion of the lower end of the trachea. The upper lobe of the right lung was atelectatic, and there was moderate bronchiectasis throughout this lung. The superior vena cava was narrowed to about one-fourth its normal size by direct invasion of its posterior wall by carcinoma entering from an adjacent lymph node. The azygos vein was considerably dilated. There were metastases in the liver, kidneys, and spleen.

Comment.—This case is an example of invasion of the superior vena cava by a malignant neoplasm, resulting in partial occlusion. With x-ray therapy there was a reduction in size

of the mediastinal tumor and partial relief of the superior vena caval obstruction. Death was in no way attributable to the superior vena caval syndrome.

CASE 3.—*Complete Superior Vena Caval Obstruction Due to Bronchogenic Carcinoma.*—R. L. (B66335), a 41-year-old white man, had been suffering from dyspnea of increasing severity and loss of weight for six and one-half months when he entered a sanatorium with the diagnosis of tuberculosis of the right lung. Pneumothorax was attempted but was unsuccessful. A short time later severe cough developed. On one occasion there was slight hemoptysis. Bronchoscopic examination disclosed narrowing of the right main bronchus, and the patient was transferred to Gallinger Municipal Hospital for further study. On this admission the diagnosis was bronchogenic carcinoma in an inoperable stage. He was discharged unimproved.

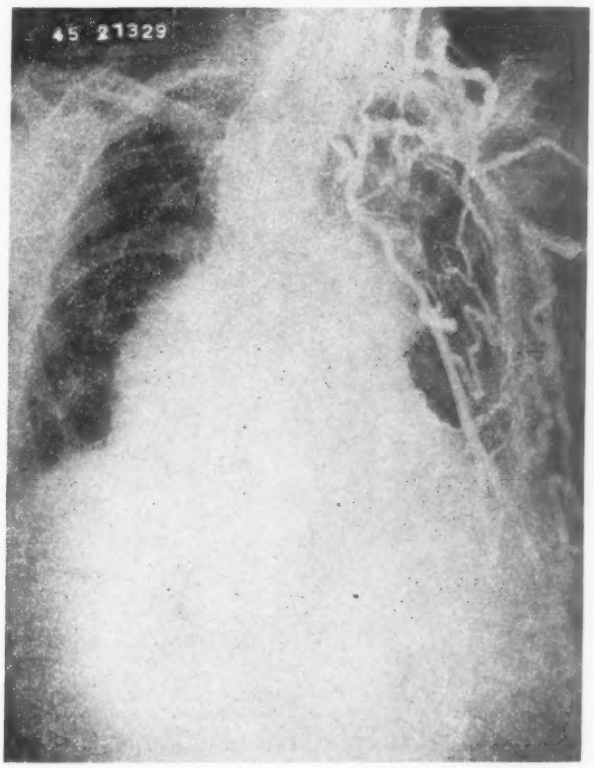

Fig. 16.—Phlebogram made by injecting Diodrast into left antecubital vein in same case illustrated in Figs. 14 and 15 (Case 5 of series of illustrative cases), showing extensive collateral network of left side of chest anastomosing with veins on right side.

One month later the patient returned to the hospital because of intractable pain in the right side of the chest. He had lost greatly in weight and strength. His cough had become productive of foul sputum. He had also noticed occasional swelling of the face and neck.

The patient was emaciated, and there was moderate swelling of the face and neck. The neck veins were abnormally prominent, and the superficial veins of the chest and abdomen were greatly distended. Dullness and diminished tactile fremitus and breath sounds were found over the entire right lung. The venous pressures were 325 mm. and 335 mm. in the right and left arms, respectively. The pressure rose 20 mm. on each side with exercise of the hand. The femoral venous pressure was 80 millimeters. X-ray examination of the chest showed a homogeneous opacity of the upper two-thirds of the right lung with several fluid-

containing cavities in the right upper lobe. A phlebogram was made by injecting Thorotrast into a vein of the left arm. In this film the left axillary, subclavian, and innominate veins were dilated. There were numerous small collateral veins in the region of the left shoulder. There was a reflux of some of the contrast medium into the left internal jugular and right innominate veins. The superior vena cava was patent but considerably narrowed (Fig. 8).

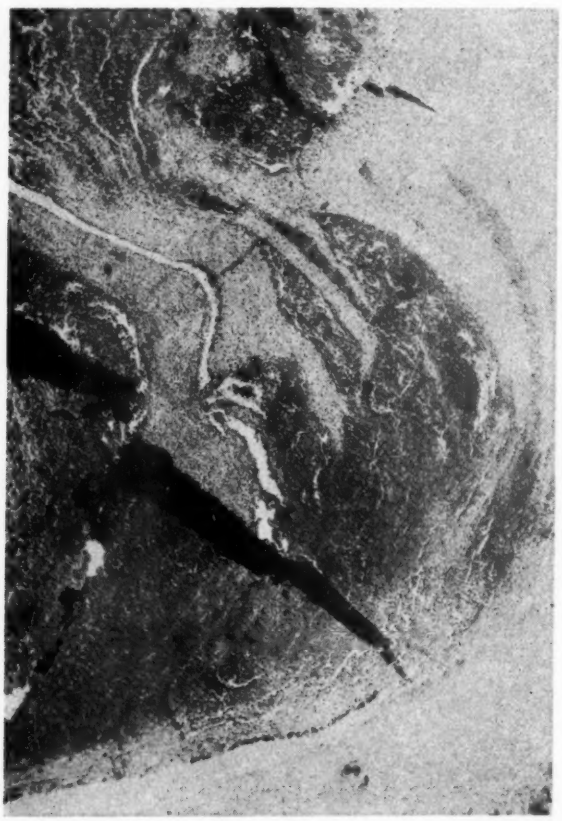

Fig. 17.—Photomicrograph of section of superior vena cava of Case 3 of series of illustrative cases showing collections of tumor cells at edge of thrombus filling vena cava.

The patient's course was one of progressive weakness and emaciation, with death from inanition. Necropsy disclosed a large solid tumor involving the entire superior mediastinum and obliterating the right main bronchus. The superior vena cava traversed this mass and was about 5 mm. in diameter and completely filled by thrombus. There were large bronchiectatic abscesses throughout the right lung. Metastases were found in the liver, spleen, and right adrenal gland. On microscopic examination, the tumor proved to be a bronchogenic carcinoma. The wall of the superior vena cava was extensively invaded by the tumor cells, many of which were included in the thrombus (Fig. 17).

Comment.—This was a case of invasion and gradual constriction of the superior vena cava by a malignant neoplasm. At the time a phlebogram was made the superior vena cava was greatly narrowed but patent throughout. Later it was completely occluded by a thrombus. However, the collateral channels to the inferior vena caval system were adequate, and the occlusion of the superior vena cava did not appear to contribute to the patient's death.

CASE 4.—*Superior Vena Caval Syndrome Due to Aortic Aneurysm With Perforation Into Superior Vena Cava.*—F. G., a 41-year-old white man, was admitted to the Georgetown University Hospital with the chief complaint of swelling of the face and neck. Two weeks before, he had suddenly developed dyspnea, a brassy cough, hoarseness, and edema of the face and neck. The symptoms had increased in severity. Associated with the facial edema there was generalized pain in the face. He had become drowsy and lethargic and had experienced difficulty in swallowing. The past history was negative except that the patient had received antisyphilitic treatment two years before admission.

On examination the patient was orthopneic and somnolent. His face and neck were greatly swollen (Fig. 18). The skin of the upper half of the body was purple-red, while the skin of the lower half of the body was quite pale. The veins of the neck, shoulders, front and back of chest, and epigastrium were greatly distended. There were patches of ecchymosis along the costal margins. The heart sounds were normal, but there was dullness to the right and left of the upper part of the sternum. The venous pressure measurements were as follows:

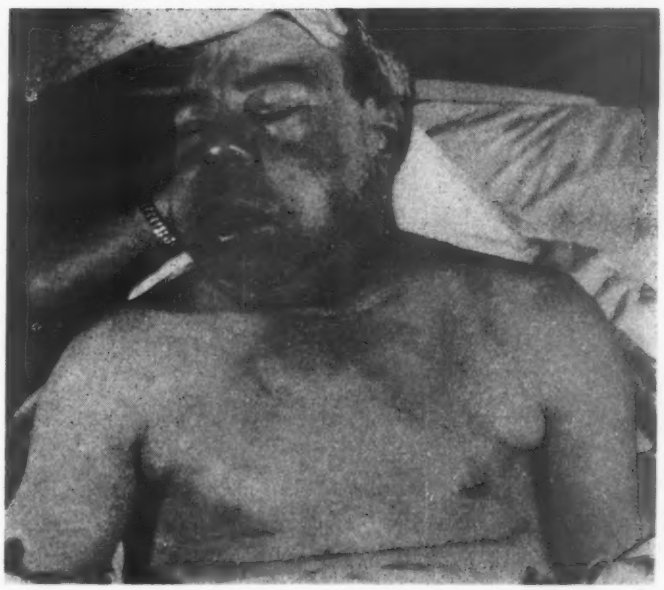

Fig. 18.—Patient of illustrative Case 4, showing massive edema of face, neck, chest, and arms and dilated veins on chest wall.

right arm, 560 mm.; left arm, 540 mm.; femoral, 110 millimeters. The arm-to-tongue circulation time was 15 seconds. While the venous pressure was being measured in the arm, special note was made of the fact that the column of saline in the manometer did not show oscillations synchronous with the arterial pulse. There was nothing unusual about the color of the venous blood drawn from the arm. The blood Kahn reaction was 4 plus. X-ray examination of the chest showed a large saccular aneurysm with displacement of the heart downward and to the left. The aneurysm occupied the entire area between the sternum and the vertebral column. There was a small amount of fluid at the right base. Fluoroscopic examination following a swallow of barium showed almost complete obstruction of the esophagus due to compression by the aneurysm. A phlebogram was made by injecting 35 per cent Diodrast into the left external jugular vein. This showed dilatation of the external jugular with reflux of the contrast medium into the left internal jugular vein. The Diodrast extended as far as the upper part of the innominate vein. Collateral veins were present in the left cervical area and in the upper thoracic region on both sides.

The patient lived for about a week after entering the hospital. During this time the edema, cyanosis, and dyspnea increased. The temperature and pulse were normal. The arterial blood pressure was persistently low, ranging from 90/80 to 106/70.

Necropsy revealed an aneurysm, 30 cm. in diameter, involving the arch of the aorta. The aneurysm compressed the trachea, esophagus, and superior vena cava. The left innominate vein was thrombosed to the point of entrance into the superior vena cava. There was a large, slitlike communication between the aneurysmal sac and the superior vena cava.

Comment.—Judging from the necropsy findings in this case there must have been partial obstruction of the superior vena cava for a considerable period due to compression by a large aortic aneurysm. The sudden onset of pain and edema of the face and neck, cyanosis of the upper half of the body, and dyspnea announced the development of a communication between the aneurysm and the superior vena cava. The clinical picture was one of the superior vena caval syndrome in its most extreme form, and death apparently was attributable to the interference with the flow of blood through the superior vena cava. There was no aortic regurgitation in this case, and it is noteworthy that aortic regurgitation was present in only three of the twelve cases of aortic aneurysm in this series. Another case of aneurysm of the aorta with perforation into the superior vena cava is included in this series. This case has been reported elsewhere in detail[10] and was similar in all respects to the one reported here.

CASE 5.—*Superior Vena Caval Obstruction Due to Mediastinal Mass of Unknown Nature.*—H. J. (B93141), a 52-year-old Negro woman, complained of cough and a choking sensation in the throat of eighteen months' duration. There had also been substernal discomfort, unrelated to effort, for this same period. Six months after the onset of these symptoms slight dyspnea and edema of the ankles developed. During the ensuing year the dyspnea became progressively more severe; and one month before admission to the hospital the face, neck, and right breast became swollen. There had been a loss of 40 pounds during the year prior to admission. The cough had increased in severity.

On examination, the patient was found to have severe dyspnea. The face, neck, chest wall, and right breast were moderately edematous, and the lower extremities showed slight edema. The veins of the neck and upper part of the anterior chest wall were prominent. The heart sounds were normal, and the arterial blood pressure was 130/90 in each arm. Because of the patient's dyspnea, the venous pressure measurements were made with the head of the Gatch bed elevated about 30 degrees, so that it was expected that the femoral venous pressure would be somewhat higher than usual. The venous pressure in the right arm was 525 mm. and rose to 650 mm. with exercise of the hand. The venous pressure in the left arm was 597 mm. and rose to 722 mm. with exercise of the hand. Application of a constricting band to the lower part of the chest caused a rapid rise in the venous pressure. The column of saline in the manometer rose with inspiration and fell with expiration. The pressure in the femoral vein was 270 millimeters. The arm-to-tongue circulation time was 22 seconds on the right, 25 seconds on the left. The blood Kahn reaction was 2 plus. A roentgenogram of the chest that had been made at another hospital at the time of onset of the patient's illness showed nothing abnormal except dilatation of the ascending aorta. X-ray examination at the time of admission to Gallinger Municipal Hospital disclosed a round opacity 9 cm. in diameter at the right border of the heart. The superior vena cava was dilated, and the heart and knob of the aorta were displaced to the left. On fluoroscopic examination the mediastinal mass appeared to be continuous with the ascending aorta and seemed to pulsate. A swallow of barium did not reveal displacement or obstruction of the esophagus. A phlebogram was made by injecting 70 per cent Diodrast into the right external jugular vein. There was dilatation of the right innominate vein and superior vena cava. The vena cava was dilated and no definite point of obstruction was shown; from the point where it would enter the right atrium, the contrast medium coursed in a narrow line which followed the right border of the mediastinal mass. There was a similar narrow line extending from the lower end of the superior vena cava along the left border of the mediastinal mass. There were collateral channels in the cervical and lower anterior thoracic regions (Figs. 14 and 15).

At the time of this writing the patient has been under observation in the hospital for five and one-half months. During the first part of this period there was a great increase in the edema and development of pleural effusion on the right side. The cough, dyspnea, and substernal discomfort became more severe. Intensive treatment with diuretics was then started, and the edema gradually disappeared. Coincidentally the cough and dyspnea lessened. The collateral veins over the chest wall, especially the lateral thoracic veins, became larger and more numerous (Figs. 16 and 19). Large, tortuous superficial abdominal veins have appeared (Fig. 20). The venous pressure measurements were repeated three and one-half months after admission and showed a marked lowering of the venous pressure in the arms (418 mm. as compared to 525 mm.).

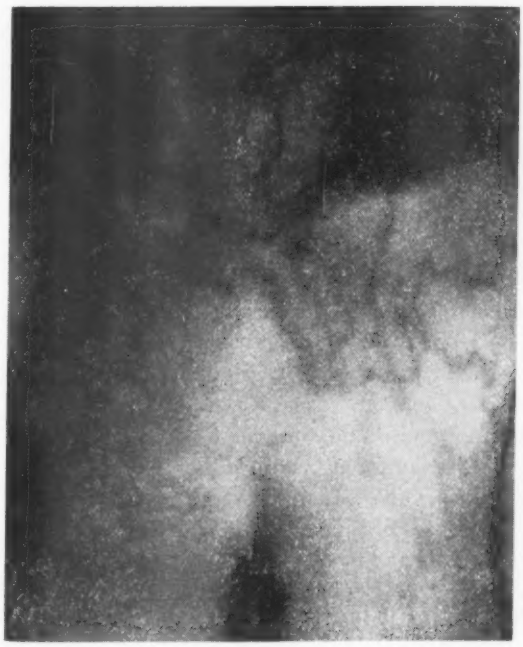

Fig. 19.

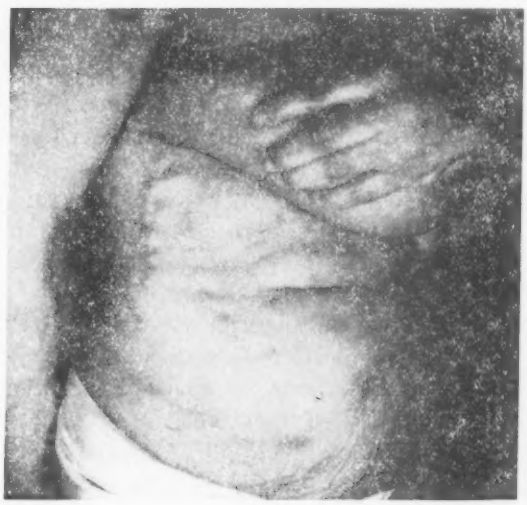

Fig. 20.

Fig. 19.—Infra-red photograph of patient in Case 5 of illustrative series, showing venous network in left side of neck and chest.

Fig. 20.—Infra-red photograph of right side of chest and abdomen of patient of Case 5 of series of illustrative cases, showing dilated tortuous veins of chest and abdomen.

Comment.—This is a case of complete obstruction of the superior vena cava below the point of entrance of the azygos vein. The distribution of the collateral veins on the abdomen confirms this fact. The paradoxical fluctuation with respiration of the venous pressure in the arms and the rise of venous pressure when a constricting band is applied to the lower part of the chest are additional proof of this point.

CASE 6.—*Superior Vena Caval Obstruction Due to Mediastinal Metastases From Carcinoma of the Ovaries.**—L. R. (A3483), a 47-year-old white woman, was admitted to the hospital complaining of dyspnea and swelling of the face and neck. Five weeks before admission her neck had been forcibly flexed, and the following day she had noticed swelling of the face and neck. Four days before admission she had become dyspneic and had noticed distention of the veins in the neck and over the chest.

*Previously reported.[16]

The patient was extremely dyspneic, and the upper half of the body was cyanotic. The face, neck, arms, and chest wall were edematous. The superficial veins of the chest were distended. There were signs of pleural effusion on the right side. Fluoroscopic examination of the chest revealed that there was fluid in both pleural cavities and an abnormal shadow in the anterior superior mediastinum. Bilateral thoracentesis yielded chyle.

The patient improved temporarily, apparently mainly as the result of the pleural aspirations. Death occurred on the eleventh hospital day during a sudden attack of severe orthopnea.

At necropsy bilateral chylothorax and chylopericardium were found. The thoracic duct was obstructed by thrombus and tumor cells which originated from bilateral carcinoma of the ovaries. The subclavian, internal jugular, and innominate veins, as well as the superior vena cava, were thrombosed. Tumor cells had invaded the vein walls and could be seen within the thrombus in various locations. There were also metastases to the mediastinal lymph nodes.

Comment.—In this case there was thrombosis of the superior vena cava and all its main tributaries due to neoplastic invasion of the vein walls by way of the thoracic duct.

DISCUSSION

In this series of cases of the superior vena caval syndrome the main causes were aneurysm of the ascending aorta, bronchogenic carcinoma, metastasis to the mediastinum from carcinoma in other locations, and malignant lymphoma. This finding agrees with the reports in the recent literature. Thrombosis of the superior vena cava has been given undue emphasis as the result of a review of this subject by Ochsner and Dixon.[17] In many of the reports in the older literature, substantial proof of thrombosis of the vena cava was lacking. Actually this entity is rare and occurs for the most part in cases in which the vena cava is invaded by neoplastic cells. With aneurysm the syndrome of compression of the superior vena cava is complicated at times by the development of a communication between the aneurysm and the vena cava. In such cases the manifestations of superior vena caval syndrome will appear or, if already present, will be intensified.

When obstruction of the superior vena cava is complete, or nearly so, the diagnosis usually is evident from the history and physical findings. When obstruction develops suddenly, the onset is characterized by severe edema and cyanosis in the regions drained by the superior vena cava and by extreme dyspnea. The edema results from the great increase in venous pressure. However, there are cases in which there is no edema in spite of the fact that the venous pressure is considerably above 200 millimeters. At times the edema is so massive and sudden as to cause pain from distention of the skin. It is aggravated when the patient is recumbent because in this position the venous pressure is higher. It tends to decrease when the patient is upright and as the result of development of collateral venous channels. The cyanosis is peculiarly reddish and is due to distention of the capillaries and to the tremendous increase in the volume of blood in the veins emptying into the superior vena cava. These same factors explain the appearance of numerous subcutaneous venules, noted especially in the region of the sternum and along the rib margin. Many theories have been advanced for the explanation of the dyspnea in this syndrome but none is completely adequate. The most logical would seem to be that venous stasis in the respiratory center results in the accumulation of metabolites lo-

cally which stimulate the center and thereby provoke dyspnea.[18, 19] The dyspnea may be intensified as the result of edema of the upper respiratory passages, which may also cause hoarseness and cough. In like manner edema of the pharynx may occasionally cause dysphagia. As a result of the high pressure in the cerebral veins when the superior vena cava is suddenly occluded, there may be drowsiness or stupor and occasionally convulsions and loss of consciousness. In the unusual event that a patient survives sudden occlusion of the superior vena cava, a collateral circulation develops which is comparable to that seen in gradual occlusion.

When the superior vena cava is gradually obstructed, a collateral circulation develops more or less concurrently, thereby modifying the clinical picture mainly because the blood which tends to be trapped in the superior vena caval system is distributed in a larger venous bed. The pattern of the collateral veins varies according to the point of obstruction of the superior vena cava.[20] When the obstruction is above the azygos vein, this takes over the function of the superior vena cava and the system of collateral channels is less elaborate and is deeply situated for the most part. However, the veins of the neck, shoulder girdle, and upper part of the thorax are prominent. When the obstruction is below the azygos vein or includes it, the blood from the superior vena caval system reaches the heart by way of the inferior vena cava. This requires the development of a more elaborate collateral circulation which is particularly extensive in the superficial veins of the thorax and abdomen. Pleural effusion may develop when obstruction is in this location and is more often on the right side.[17] Dyspnea, cyanosis, and edema are less prominent with gradual obstruction and may be present only when the patient exercises or is recumbent, either circumstance having the effect of elevating the venous pressure in superior vena caval occlusion.

Partial obstruction of the superior vena cava, as opposed to complete obstruction, is seldom recognized by means of physical examination alone. Awareness of the possibility of partial obstruction in a patient who has a mediastinal mass is the first requisite to the recognition of the syndrome. Confirmation of its presence is obtained by means of venous pressure measurements.

Comparison of measurements of venous pressure in the antecubital and femoral veins is important for substantiation of the diagnosis of the superior vena caval syndrome. In any case the pressure in the antecubital vein is significantly higher than in the femoral vein. The femoral venous pressure is almost always normal (below 150 mm.), and when it is higher than normal some other factor than the obstruction of the superior vena cava is responsible. The increased volume of blood entering the inferior vena cava by way of collateral vessels from the superior vena cava is not of itself a cause for elevation of the pressure in the femoral vein. The height of the venous pressure in the upper extremity varies according to the degree of obstruction of the superior vena cava, the acuity of onset, the location of the obstruction (whether above or below the azygos vein), and the extent of development of the collateral circulation. Repeated measurements are valuable for following the course of

the syndrome. Lowering of the venous pressure indicates that the collateral circulation has become more adequate or, in the case of a radiosensitive mediastinal tumor, that the reduction in size of the tumor by x-ray therapy has resulted in a decrease in the obstruction of the superior vena cava. An increase in the venous pressure signifies that the degree of obstruction has become more nearly complete or that the obstruction has involved a main tributary of the superior vena cava.

Measurements of circulation time are relatively less valuable in the study of the syndrome. In the majority of cases the arm-to-tongue circulation time is within normal limits or is disproportionately low as compared to the height of the venous pressure. Prolongation of the circulation time does not necessarily mean that the rate of flow of the blood in the veins is slow. More often the prolongation is an expression of the devious route which the blood from the arm must follow in order to reach the heart.

Phlebography in the superior vena caval syndrome has litle practical value but is a nice method for demonstrating that obstruction exists and, at times, for locating it. The pattern of the collateral circulation can usually be visualized with great accuracy.

A special type of the syndrome is seen when an aneurysm of the aorta communicates with the superior vena cava. In these cases the onset is explosive with severe dyspnea and edema and cyanosis of the upper part of the body. Actually the diagnosis depends on *the sudden onset of severe manifestations of the syndrome in a patient with aortic aneurysm.* Signs ordinarily associated with arteriovenous fistula, such as thrill, bruit, and wide pulse pressure, are not usually found. Thrill and bruit are absent probably because the communication is often large. The volume of blood reaching the peripheral arteries is diminished because a large part of the blood leaving the left ventricle is shunted from the aorta into the superior vena cava. The arterial blood pressure in the extremities, therefore, tends to be diminished. In the two cases included in our series it was noted that blood from the antecubital vein looked typically venous, whereas it might have been anticipated that it would be more like arterial blood (brighter red). Probably this was due to the fact that the blood was drawn from veins that were some distance from the arteriovenous communication. Blood from the external jugular vein might have been more arterial in color. On the other hand, it is possible that so little blood reaches the lungs that all of the blood, both in the arteries and veins, is suboxygenated. Such a state might be revealed by simultaneously withdrawing arterial blood for comparison. Further, it was noted that the column of saline in the venous pressure manometer did not pulsate synchronously with the arterial pulse when the venous pressure was being measured in the arm. Again, the explanation probably lies in the fact that the antecubital vein is too distant from the fistula for pulsations to be transmitted or that the pulsation is dissipated as a result of engorgement of the veins.

We have not included a discussion of treatment in the analysis of our cases. Except for x-ray therapy in patients with radiosensitive mediastinal tumor, treatment is of little avail. The administration of oxygen, the use of diuretics,

and venesection are of some value for the relief of symptoms. There are reports[1, 17, 21] which suggest that surgical exploration of the mediastinum should be employed more often for severe obstruction of the superior vena cava with a view to decompressing the mediastinum and possibly removing scars or adhesions from the vicinity of the superior vena cava. This would apply mainly for cases, however, in which there is no evidence of an obstructing mass.

SUMMARY AND CONCLUSIONS

1. The data from 35 cases of superior vena caval syndrome have been presented.

2. Aneurysm of the ascending aorta, bronchogenic carcinoma, malignant lymphoma, and carcinoma with metastasis to the mediastinum are the main causes of the syndrome. Simple thrombosis of the superior vena cava is very rare.

3. The principal symptoms and signs of the syndrome are edema and cyanosis in the upper part of the body, dyspnea, and dilated veins indicative of the collateral circulation. Many other symptoms may be present depending on the nature of the underlying disease.

4. Comparison of measurements of the venous pressure in the upper and lower extremities is the best method for establishing the diagnosis of obstruction of the superior vena cava. This may be the only practical method for recognizing that the vena cava is partially obstructed. The venous pressure in the arms is significantly higher than the femoral venous pressure.

5. The arm-to-tongue circulation time may be normal in spite of the fact that the venous pressure is quite high. If prolonged, it is usually less than might be anticipated from the height of the venous pressure.

6. Phlebography demonstrates that obstruction of the superior vena cava is present and, at times, localizes the point of obstruction.

7. In two cases of aortic aneurysm the superior vena caval syndrome was produced by communication between the aneurysm and the superior vena cava. This condition should be suspected when the syndrome develops explosively in a patient with aneurysm of the aorta. The usual features of arteriovenous communication, such as thrill, bruit, and an increase in pulse pressure, may not be present.

8. X-ray therapy of radiosensitive mediastinal tumors may decrease obstruction of the superior vena cava. Surgical exploration of the mediastinum may be of value in cases in which lack of evidence of the cause of the obstruction holds promise of a remediable condition such as obstruction by adhesions.

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A STUDY OF THE PROTHROMBIN TIME IN NORMAL SUBJECTS AND IN PATIENTS WITH ARTERIOSCLEROSIS

A Preliminary Report

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THE literature abounds with investigative work dealing with the blood prothrombin in various diseases. However, little work has been reported regarding possible changes in coronary disease. In 1941, Doles[1] reported that he had found the prothrombin time to be prolonged in a few cases of acute coronary occlusion he had tested, and in 1943 he[2] reported his findings in thirteen cases. The prothrombin time was found to be prolonged before the attack and increased still further twelve to forty-eight hours later. A return to normal was demonstrated in several of these cases after vitamin K therapy. Shapiro[3] also reported hypoprothrombinemia in acute coronary occlusion. We have been able to find no other reports in the literature dealing with the prothrombin time in various phases of coronary sclerosis. Because of the meager amount of investigative work previously done, and because of the potentialities of the problem, an intensive study was begun to determine what part, if any, the prothrombin mechanism plays in coronary thrombosis.

METHODS

Using the method of Shapiro,[3] one is able to eliminate most of the usual pitfalls in prothrombin determination. In addition, a carefully prepared and standardized thromboplastin is essential. Dr. Overman's* preparation from desiccated cat lung has been found to be satisfactory. Each time prothrombin estimations were made, the blood of a normal person was used as a control. Dilute and undiluted plasma determinations were checked two or three times, and the control specimen was rechecked after each series. The chief advantage of Shapiro's method is that it employs both dilute and undiluted plasma for the determination of the prothrombin time. In the dilute determinations a 1:8 saline solution of plasma is used. This method is the most exact and duplicate determinations check with accuracy. In our experience the dilute plasma is a more sensitive indication of slight changes in the prothrombin time than is whole plasma.

As a corollary measure to rule out hepatic damage, a cephalin flocculation test was done on all patients.

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*The thromboplastin used in this study was supplied through the courtesy of Dr. Ralph S. Overman of The Maltine Company.

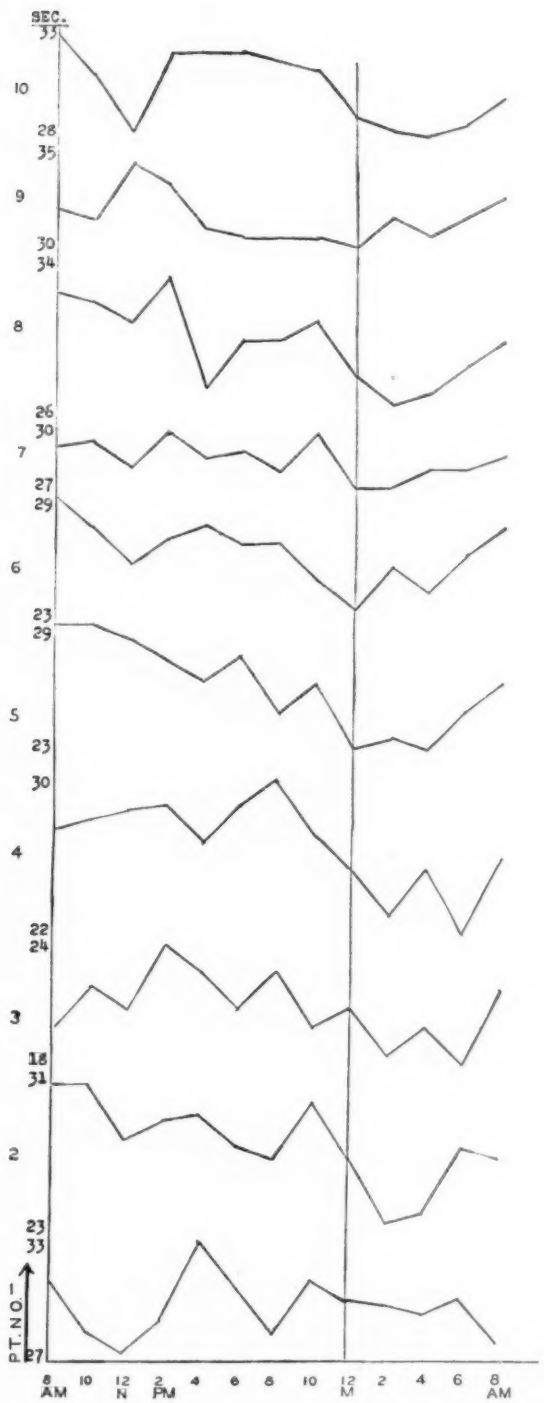

Fig. 1.—Two-hourly dilute prothrombin times in ten patients with coronary arteriosclerosis.

VARIATIONS IN PROTHROMBIN TIMES

Diurnal Variations.—A group of ten patients with coronary arteriosclerosis was chosen to determine whether there were diurnal variations in the prothrombin time. The tests were done every two hours during a twenty-four-hour period. For purposes of comparison, six normal males from the house staff of the Post-Graduate Hospital also were tested. Eight of the patients had had myocardial infarctions from one week to several months before study, two were in the hospital with cerebral accidents and had myocardial damage as judged by the electrocardiograms.

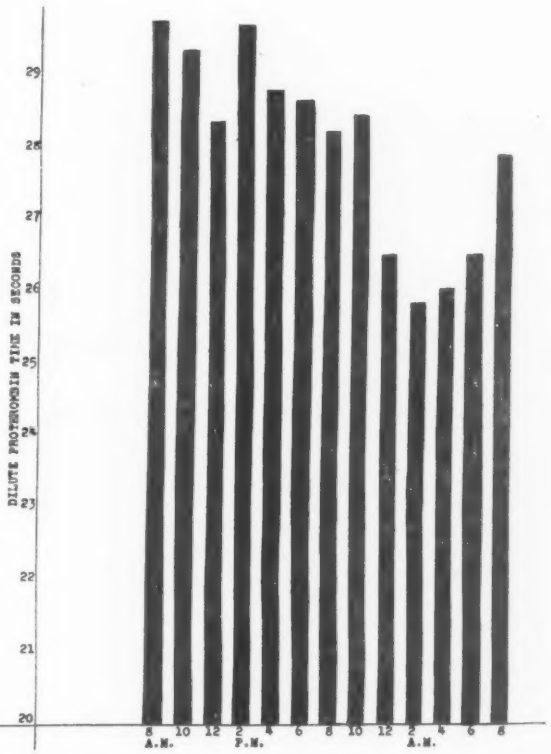

Fig. 2.—Average of dilute prothrombin times of ten patients with coronary arteriosclerosis.

The diluted plasma revealed changes which appear to be clinically and statistically significant. No significant changes were observed in the undiluted plasma prothrombin time other than a variation of a second or two above or below the normal of twelve to fourteen seconds.

Fig. 1 illustrates a curve of the two-hourly dilute prothrombin times of the ten patients. A line drawn through the values plotted at midnight accentuates the beginning drop in time which several of these patients manifested. An upswing and a tendency to return to the normal is seen at 6:00 A.M. and continues to 8:00 A.M., when the series was stopped.

Fig. 2 illustrates the average of the dilute prothrombin times of the ten patients taken at the time intervals indicated. Again, one can see quite well the drop in prothrombin time in the late hours of night and early morning with the gradual tendency to return to normal.

Fig. 3 illustrates the comparison between the average two-hourly dilute prothrombin times of the normal male and the patients. Here there is seen no significant change among the normal persons, whereas the lower curve indicates quite clearly a drop in prothrombin time among the arteriosclerotic patients.

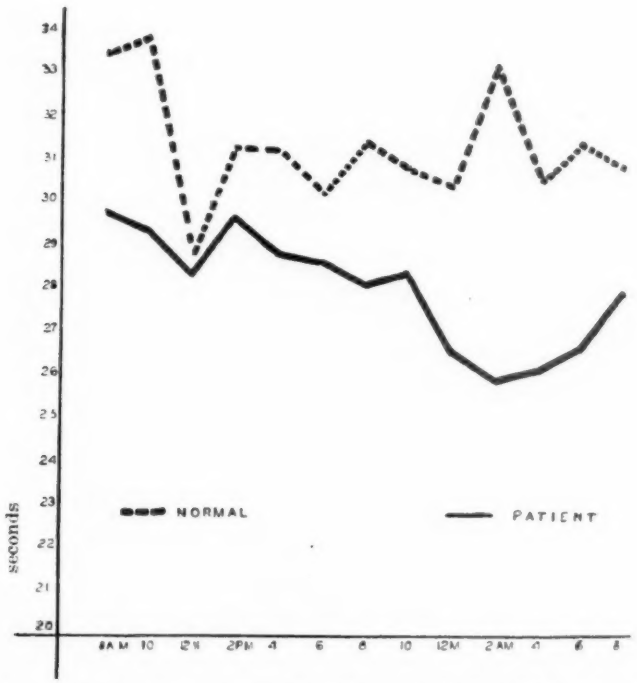

Fig. 3.—Comparison between dilute prothrombin times of six normal males and ten patients with coronary arteriosclerosis.

Effect of Exercise.—The effect of exercise upon the prothrombin time of the normal male and the patient with coronary arteriosclerosis was also observed. Five normal males and five patients recuperating from coronary thrombosis were chosen. The control subjects were required to raise their extended bodies from the floor by the use of their arms only. The patients rose from the flat position in bed to touch their toes. Both exercises were done until a state of fatigue existed. Prothrombin estimations were done before exercise, and three, thirty, and sixty minutes afterward. In neither group did the prothrombin time, dilute or undiluted, vary by more than a second or two in any individual tested.

Monthly Prothrombin Time Estimations in Patients With Coronary Sclerosis.—In a further study of patients with arteriosclerotic heart disease, two groups were observed. A series of 28 patients with coronary sclerosis and

anginal syndrome were tested. Prothrombin time estimations were made every month as they returned to the clinic. Four determinations were done on each of five patients, whereas the remainder have been tested from one to three times. At the present time no definite trend toward shortening or prolongation of the prothrombin times is yet discernible in this group.

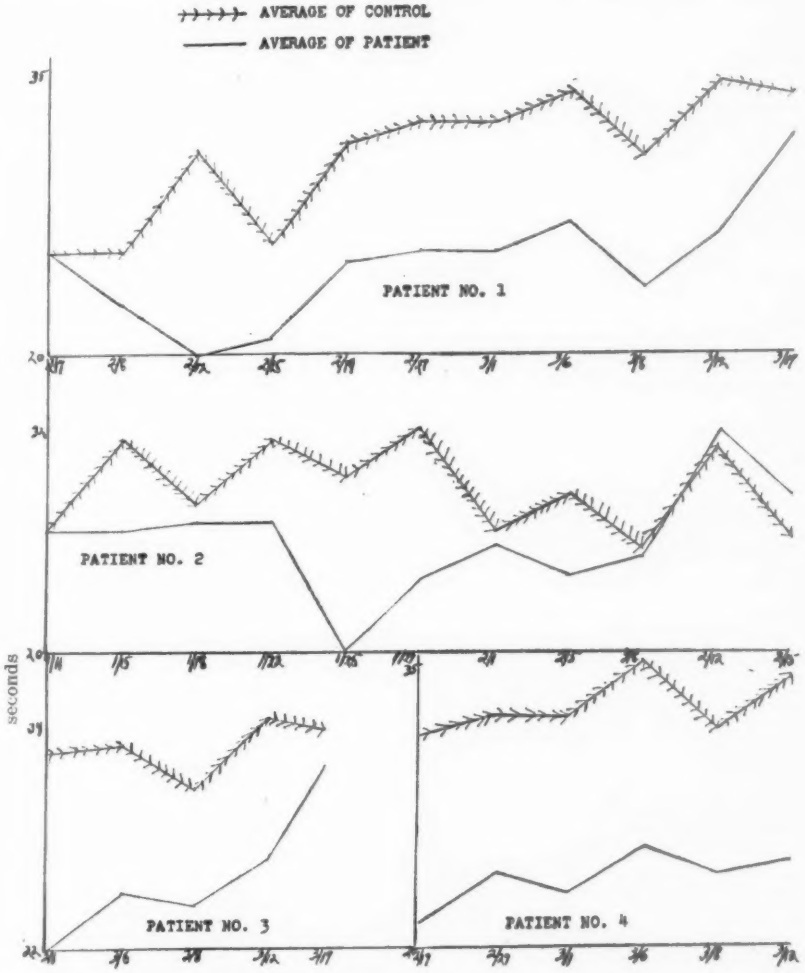

Fig. 4.—Sample prothrombin time curves of four patients with coronary arteriosclerosis during the six-week hospitalization period and comparison curves of controls.

Acute Coronary Occlusion.—A second group of patients were studied who had been hospitalized because of acute coronary occlusion. Prothrombin estimations have been done in 13 cases thus far. Five have been observed from the onset. The remaining eight were brought into the hospital from one day to three weeks after the initial seizure. Determinations were done immediately in those seen in the midst of the attack. Prothrombin time studies were made every third day for the six-week hospitalization period.

One observation has been that the prothrombin time did not change during the initial period of pain. But a change in the dilute prothrombin time did appear within twenty-four to seventy-two hours. Whereas the undiluted prothrombin determinations changed either little or not at all, the dilute fraction showed shortening of the time from one to as much as ten seconds. This has been the finding in all but three cases.

The curves of four patients have been plotted along with curves of the normal controls studied concomitantly (Fig. 4). Patients 1 and 2 at the top show how the dilute prothrombin time remained normal during the attack and continued to do so for several weeks until a gradual return to normal was observed. The lowermost curves are those of patients seen several days after the attack. Here, again, the prothrombin time is shortened during the period of observation. The value in Patient 4 has not returned to normal even after six weeks. No medication other than sedatives and catharties was used. Digitalis was required in five cases but, fortunately, the change in the prothrombin time came before its administration, so that no effect can be attributed to it. Furthermore, a return to normal was noted even in these cases.

Cephalin Flocculation Test in Patients With Coronary Sclerosis.—Only one patient revealed a 3 plus Hanger reaction. He was a patient with anginal syndome, and his prothrombin time was normal.

SUMMARY AND CONCLUSIONS

1. The dilute prothrombin time has revealed changes in patients with coronary arteriosclerosis that have not been demonstrated by the ordinary undiluted method. This may be due, Shapiro[3] states, to an anticoagulant factor in undiluted plasma which is inactivated by dilution.

2. In diurnal studies of the prothrombin time there is a tendency toward shortening in the dilute fraction in the late hours of the night and in the early morning in patients with coronary arteriosclerosis. There is no significant change in normal males.

3. Exercise apparently had no effect on the prothrombin times of the small group of arteriosclerotic patients tested.

4. Patients with coronary sclerosis and anginal syndrome whom we have studied thus far reveal no outstanding alterations of the prothrombin time.

5. After the acute phase of coronary occlusion there is noted a definite trend toward shortening of the dilute prothrombin time which continues for several weeks during the period of infarction.

6. Further studies on the possible etiology and pathogenesis of these changes are being carried forward.

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NORMAL ELECTROCARDIOGRAMS IN CARDIOVASCULAR DISEASE

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THE introduction of the electrocardiograph into clinical medicine has been responsible for great progress in cardiology. Its use is now almost essential in any cardiac examination, and, when properly interpreted, the data obtained are of very great help in diagnosis and prognosis. The development of simple electrocardiographic equipment that can be operated by anyone and can even be carried into the home of the patient has, however, brought about a situation which is likely to arise whenever a new laboratory method comes into widespread use: that is, undue importance is often assigned to variations from the average normal which would be disregarded by an experienced physician, and too little importance is attached to other changes which, though slight, may nevertheless have great significance when the circumstances accompanying their development are taken into consideration.

Every study that recounts the occurrence of electrocardiographic abnormalities under conditions not previously known to produce them is of value. No less interesting are the circumstances under which the electrocardiogram may be of the normal type in spite of the presence of obvious cardiac disease. Accurate knowledge of the factors responsible for the absence of electrocardiographic abnormalities when the heart is damaged should be of great value to the practitioner when he finds a normal electrocardiogram in a case in which the symptoms and physical signs point to heart disease.

No entirely adequate study of the normal electrocardiogram is yet available, and the lack of such a study makes the interpretation of many borderline electrocardiograms very difficult. Wilson[1] pointed this out in a discussion in which he suggested that the life insurance companies could make a great contribution to electrocardiography if they would undertake a comprehensive statistical investigation of the electrocardiograms of normal people of both sexes and of all ages. It must, however, be remembered that the electrocardiogram may be within normal limits, in the sense that the different intervals and the voltages and durations of its several deflections are not individually beyond the normal range, and nevertheless suggest that the heart is abnormal because it does not display the features that would be expected under the attendant circumstances. The occurrence of right axis deviation in the electrocardiogram of a subject of pronounced sthenic habitus is so rare when the heart is normal that it should lead to the search for other evidence of one of the conditions that lead to right ventricular hypertrophy. The presence in Lead I or Lead II of T waves of very low voltage in the electrocardiogram of a patient

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who has an acute infection, or who has received digitalis, may be considered a probable deviation from the normal due to the disease or the drug, because the T waves of these leads are 3 to 4 mm. in height in the vast majority of normal electrocardiograms.

When a cardiac lesion is strongly suspected and the electrocardiogram is within normal limits, it should also be remembered that the routine use of precordial leads and the employment of esophageal leads has shown clearly that one or more of these special leads may display electrocardiographic abnormalities that would have escaped detection if they had not been taken. It must be admitted, therefore, that the electrical activities of certain fractions of the heart muscle may not be adequately represented in any of the leads now in use.

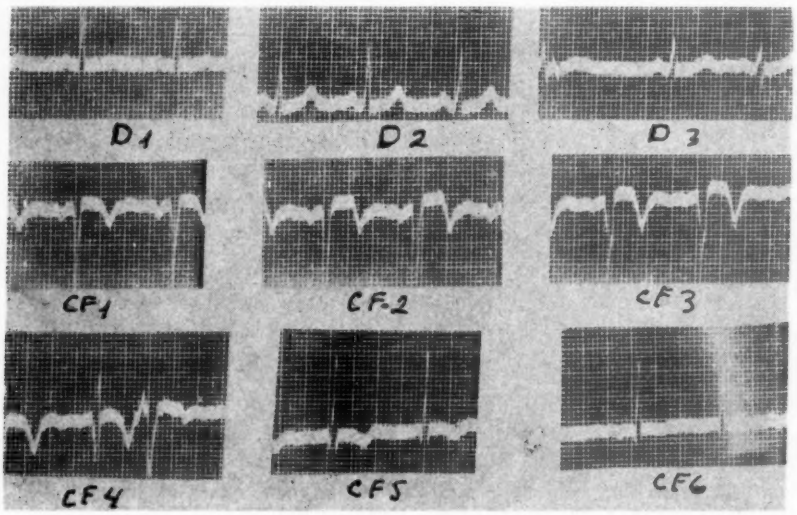


Fig. 1.—Anteroseptal myocardial infarction. The standard limb leads show only flat T waves in Lead I and a single extrasystole in Lead III.

Fig. 1 illustrates a case of infarction in which the standard limb leads showed only an unusually flat T wave in Lead I and an extrasystole. Characteristic signs of infarction were, however, present in almost all of the precordial leads. There are large QS deflections in Leads CF_1, CF_2, and CF_3; large Q waves in CF_4; upward displacement of the RS-T segment in Leads CF_2 and CF_3; and sharply inverted T waves in Leads CF_1 to CF_4, inclusive.

In Fig. 2 the only signs of infarction are a Q wave associated with a small R wave in Lead V_2 and slight terminal inversion of the T wave in Leads V_2 and V_3.*

The electrocardiograms shown in Fig. 3 are those of a subject of sthenic habitus. The first tracing (*A*) is well within normal limits. The second (*B*) was taken six months later and a few hours after the occurrence of rather indefinite substernal distress. When considered by itself, this tracing is not

*This tracing and that shown in Fig. 4 are reproduced through the courtesy of Dr. Frank N. Wilson.

definitely outside normal limits, but, when compared with the first, it shows low-voltage T waves in Lead II and more sharply inverted T waves in Lead III. The patient died suddenly one day after this electrocardiogram was taken.

The tracings of Fig. 4 illustrate a disturbance of conduction which could be diagnosed with certainty only after esophageal leads had been taken. In Lead I there is a small upward deflection, and in Leads II and III there is a

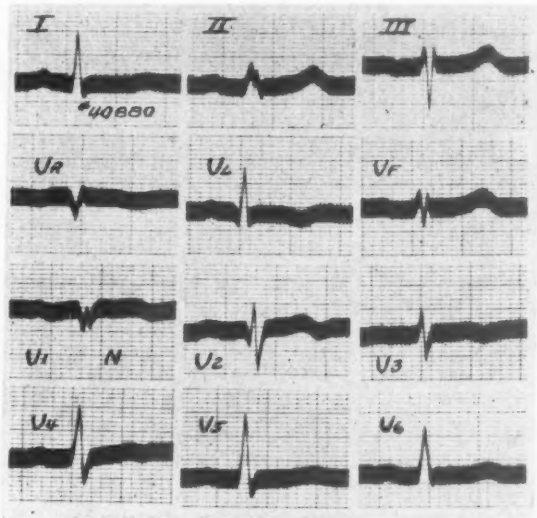
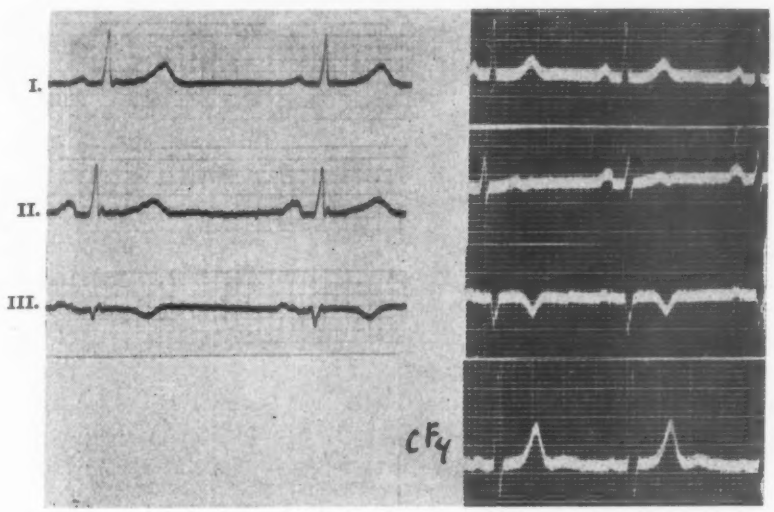


Fig. 2.—Anteroseptal myocardial infarction. The characteristic changes appear only in V_2.



A. *B.*

Fig. 3.—*A*, Normal electrocardiogram. *B*, Record on the same patient six months later, a few hours after indefinite substernal distress. The T waves are lower in Lead II and more sharply inverted in Lead III. Patient died suddenly the following day.

small downward deflection following what appears to be a normal QRS complex. A similar small deflection is visible in some of the precordial leads. The leads from the ventricular levels of the esophagus show that this component is really part of the QRS group and is due to late activation of some part of the posterior ventricular wall. The last tracing of this figure was taken during an attack of paroxysmal ventricular tachycardia.

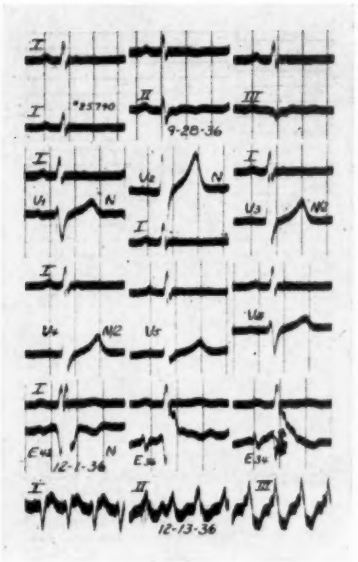


Fig. 4.

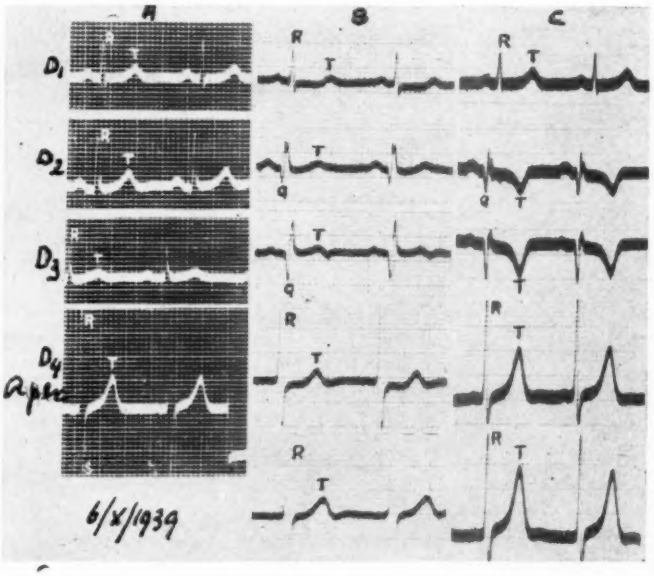


Fig. 5.

Fig. 4.—Interventricular block apparent only in the esophageal leads. E_{42}, E_{36}, and E_{34}. Record taken on Dec. 13, 1936, shows ventricular tachycardia.

Fig. 5.—*A*, Record taken during anginal pain is normal. *B* and *C*, records taken one year later, are characteristic of recent posterior myocardial infarction.

The existence of a cardiac infarct cannot be ruled out by an electrocardiographic examination even if all of the recommended precordial leads are taken. These leads are used mainly for exploring the anterior ventricular wall, and in cases of suspected infarction for the purpose of detecting involvement of this part of the heart. They are not equally useful for the detection of infarction of other regions. On the other hand, we are often justified, when the symptoms and physical signs suggest infarction, in attaching some importance to electrocardiographic changes which are not entirely characteristic of this condition and are not pronounced, particularly if they show signs in successive tracings of undergoing the sequence of modifications which infarction is known to produce. The absence in infarction of characteristic electrocardiographic patterns or of any electrocardiographic abnormalities may be due to the nonexistence of ideal leads, to the smallness of the infarct, or to the rapid development of a collateral circulation which re-establishes the integrity of the involved tissue. It is also possible, when infarction is suspected on clinical

grounds and the electrocardiogram is normal, that the pain or other symptoms were so-called prodromal manifestations of coronary occlusion rather than of the actual death of cardiac muscle.

It should also be borne in mind that many electrocardiographic abnormalities may be transient, for example those occurring in paroxysmal complete heart block and those that are observed during an attack of angina pectoris brought on by exertion, in which the changes may be present only in particular leads and only so long as the chest pain lasts.[2] These points are illustrated by the following figures:

The first tracing (A) of Fig. 5, taken on Oct. 6, 1939, when the patient was having anginal pain on exertion, is normal. The last two tracings (B and C) taken on Oct. 1 and 5, 1940, are characteristic of posterior infarction.

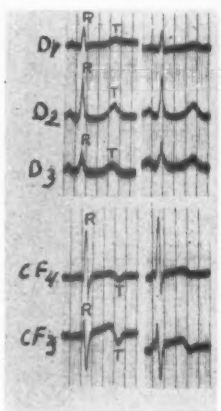


Fig. 6.

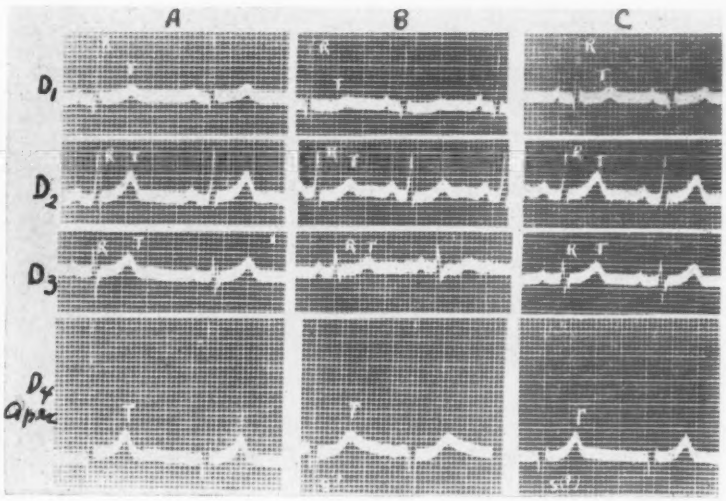


Fig. 7.

Fig. 6.—Electrocardiograms taken during anginal pain induced by exertion show changes in the T waves confined to the precordial leads.

Fig. 7.—*A*, Control; normal electrocardiogram. *B*, Record taken during angina induced by exertion shows lower and diphasic T waves. *C*, Electrocardiogram taken on recovery is again normal.

Tracings shown in Fig. 6 are those of a patient who had anginal pain on exertion. During an attack induced by effort the electrocardiographic abnormalities were confined to the precordial leads (CF_3 and CF_4).

The first tracing of Fig. 7, taken when the subject was at rest, is normal. The second, taken after exertion which induced anginal pain, shows T waves which are diphasic and of low voltage. The disturbance was transient; the third tracing is like the control.

Another transient disturbance is shown in Fig. 8. When the patient was at rest, the electrocardiogram was essentially normal apart from a shift of the electrical axis to the left and slight slurring of the R and S deflections. Im-

mediately after effort, the T waves were diphasic in Leads I and II and there was some downward displacement of the RS-T segment in these leads. In Lead III the T wave became more positive; in Lead IV the R wave became smaller. The electrocardiogram rapidly reverted to its original form.

The tracings of Fig. 9 are those of another patient who had anginal pain on exertion. On Sept. 5, 1942, effort induced left bundle branch block; on Sept. 21, 1943, when the patient was improved, it failed to do so.

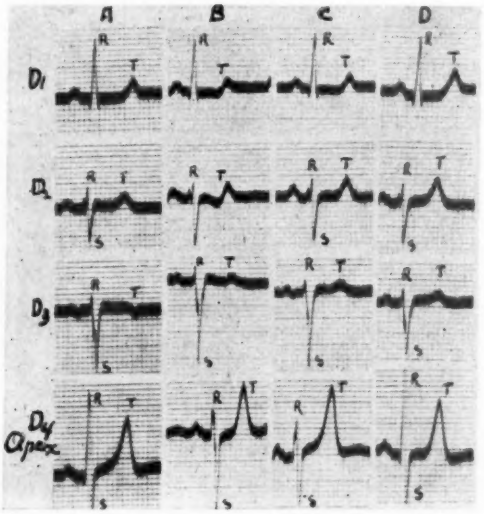


Fig. 8.—Transient changes in the T waves during angina produced by exertion. *A*, Control; *B*, *C*, and *D*, during and on recovery from pain.

Bearing in mind the complications which we have outlined, we may now turn our attention to a consideration of the circumstances under which the electrocardiogram may be normal in the presence of cardiovascular disease. It would, perhaps, be more accurate to say cardiac disease, rather than cardiovascular disease, but, since many of our studies have been made on cases of syphilitic aortitis, arterial hypertension, and arteriosclerosis, we use the more inclusive term. We have selected those cases in which the electrocardiogram was normal and have tried to analyze the factors responsible for the failure of electrocardiographic changes to occur.

We are well aware that some attention has been given to this problem in every text or treatise on the electrocardiogram. It is well known, for example, that the electrocardiogram is usually normal in patent ductus arteriosus[3] and in the initial stages of arterial hypertension. As practicing cardiologists, we have, however, felt the lack of some more systematic study of the subject. It has not been possible to restrict our investigation to cases in which the heart could be examined after death. We have, however, included only those in which indisputable objective evidence of cardiovascular disease was obtained by radiographic examination, by phonocardiographic studies, or by a series of estimations of the blood pressure.

We considered the electrocardiogram normal when it displayed the following characteristics:

The height of the P wave was less than 2 mm. (2.5 mm. in the case of children), and the duration of this deflection less than 0.10 second in all leads. The P-Q interval was not less than 0.13 and not more than 0.20 second. The QRS interval did not exceed 0.08 second. The voltage of the smallest QRS component of any lead was not less than 5 mm., and that of the largest component not more than 20 mm. in any lead. The displacement of the RS-T segment was not greater than 0.5 mm. in any lead. The voltage of the T wave was not less than 1 mm. in either Lead I or Lead II. Axis deviation was considered abnormal only when it was in the direction opposite to what would be expected on the basis of the habitus of the subject. Slight slurring of the QRS

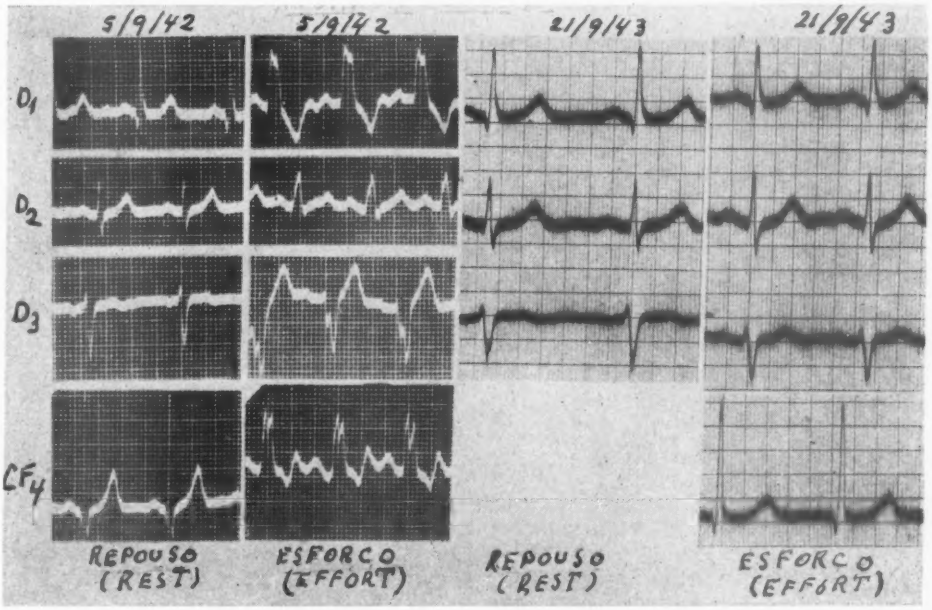


Fig. 9.—May 9, 1942: left bundle branch block appeared during angina produced by exertion. Sept. 21, 1943: exertion failed to produce electrocardiographic changes.

components was not considered abnormal. The Q-T interval was taken into consideration only when it was grossly abnormal. Isolated extrasystoles were not considered abnormal. It was not possible to consider many of the details of the abnormal electrocardiograms because, in many instances, there were doubts as to certain possible abnormalities and also because certain questionable abnormalities encountered have not, as yet, been shown to have an important significance.

We have analyzed 1,400 clinical cases. In 722 of these, the presence of cardiovascular disease was demonstrated. In 223 of these 722 cases, the electrocardiogram was within normal limits. The incidence of a normal type of electrocardiogram in the varieties of cardiovascular disease studied is shown in Table I.

TABLE I. OCCURRENCE OF NORMAL ELECTROCARDIOGRAMS IN 722 CASES OF CARDIOVASCULAR DISEASE

CLINICAL DIAGNOSIS	NUMBER OF CASES	NUMBER WITH NORMAL ELECTROCARDIOGRAMS
Hypertension	245	90
Hypertension and syphilis without clinical localization (systolic pressure between 150 and 170)	9	2
Hypertension and syphilis without clinical localization (systolic pressure above 170)	26	9
Arteriosclerosis of the aorta (without hypertension)	47	20
Coronary arteriosclerosis	51	-
Syphilitic aortitis	43	21
Syphilitic aortitis and rheumatic mitral stenosis	1	-
Aortic aneurysm (various localizations)	12	4
Aneurysm of the innominate artery	1	-
Femoral arteriovenous aneurysm	1	-
Aortic insufficiency, rheumatic	8	2
Aortic insufficiency, syphilitic	19	6
Aortic insufficiency, syphilitic and rheumatic	3	-
Aortic insufficiency, doubtful etiology	3	-
Aortic insufficiency and mitral stenosis	22	3
Aortic insufficiency and aortic aneurysm	2	-
Aortic stenosis and insufficiency and mitral stenosis	1	-
Aortic insufficiency and mitral stenosis and insufficiency	4	1
Aortic stenosis and insufficiency and mitral stenosis and insufficiency	1	-
Aortic stenosis	2	-
Rheumatic pulmonary stenosis	3	-
Tricuspid stenosis	1	-
Mitral stenosis	36	-
Mitral stenosis and insufficiency	22	2
Mitral insufficiency	22	11
Mitral stenosis and aortic stenosis	1	-
Rheumatic fever and chorea, active	2	-
Congenital heart disease		
patent ductus arteriosus	8	5
interventricular communication	3	1
pulmonary stenosis	9	1
dextrocardia	2	-
bundle branch block	2	-
tetralogy of Fallot, multiple or doubtful lesions	9	-
Dilatation or hypertrophy of heart of doubtful etiology	12	5
Dilatation or hypertrophy of left ventricle of doubtful etiology	13	8
Hyperthyroidism	20	13
Hypothyroidism	5	4
Foreign body in the heart	2	1
Cor pulmonale	1	-
Beriberi with dilatation and cardiac failure	1	1
Diphtheritic acute myocarditis	1	1
Rheumatic myocarditis	5	-
Chronic myocarditis	1	-
Chagas' disease	1	-
Chronic pericarditis	4	2
Bronchial asthma	8	5
Acute pericarditis	1	-
Diverticulum of pericardium	1	-
Paroxysmal tachycardia (out of the attack)	4	1
Bundle branch block, complete and incomplete heart blocks (unknown cause)	8	-
Angina pectoris (out of the attack)	6	2
Chronic peripheral arteritis	7	2
Total	722	223

This table gives an idea of the relative importance of an electrocardiographic examination in different types of cardiovascular disease. It is clear, first of all, that certain cardiovascular affections produce electrocardiographic abnormalities only under special circumstances. Syphilitic aortitis and aortic aneurysm apparently do so only when they are associated with narrowing of the orifices of the coronary arteries or with aortic insufficiency. Arteriosclerosis may affect chiefly the arteries of the brain or those of the kidneys; it is not likely to modify the electrocardiogram unless it involves the coronary

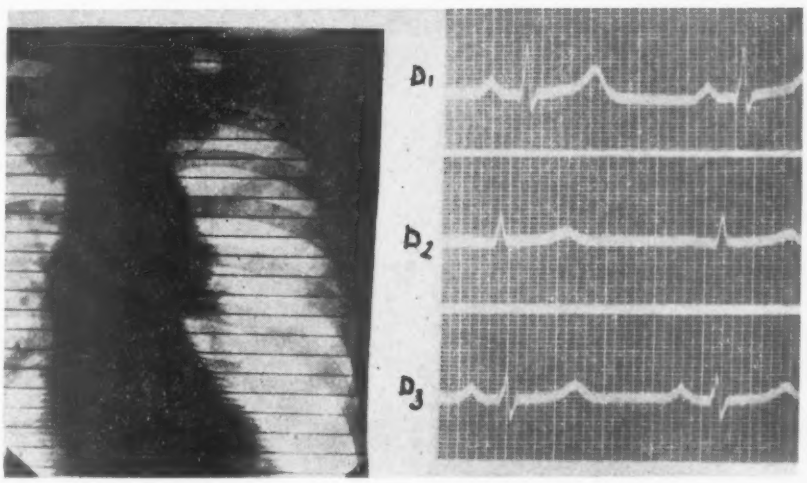


Fig. 10.—Aortic aneurysm with normal electrocardiogram.

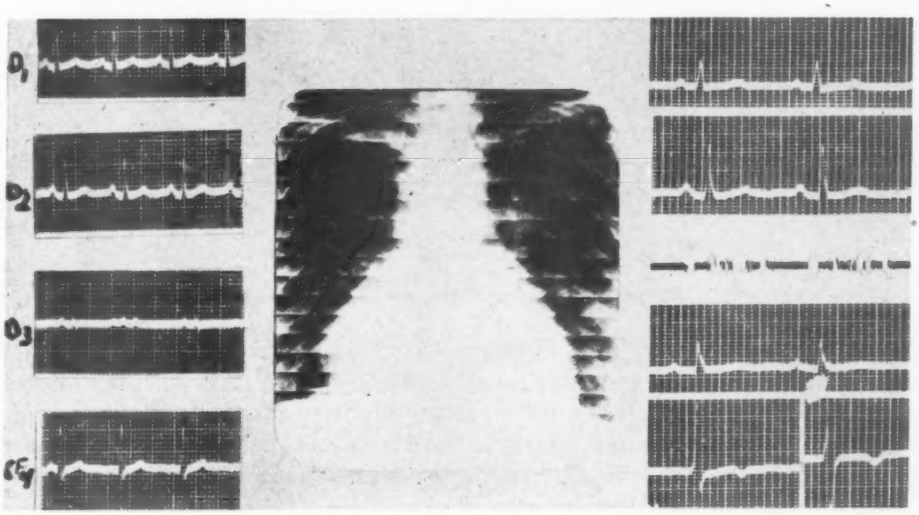


Fig. 11.—Electrocardiograms in a patient with pericarditis. First set of tracings are normal. Second set of records taken one day later show somewhat lower T waves in the standard leads and inverted T waves in CF_4

arteries. Fig. 10 illustrates a case of aneurysm of the aorta in which the electrocardiogram was normal.

In the case of pericarditis, we know that characteristic changes in the electrocardiogram are sometimes present.[4] Apparently, these changes occur only when the outer layers of the myocardium are involved or under other circumstances of a special kind which are still unknown. Displacement of the RS-T segment and inversion of the T waves are frequent, but there are also many cases in which the electrocardiogram remains normal. It is important to know this when one is confronted by a normal electrocardiogram in a case in which there is fever and enlargement of the cardiac dullness without evidence of involvement of the heart valves or other clues to the nature of the cardiac abnormality. Fig. 11 illustrates a case of pericarditis in which the first electrocardiogram was essentially normal. In the second, taken one day later, the T waves are of low voltage in the limb leads and inverted in Leads CF_3 and CF_4. The sound record shows a friction rub audible in the central precordium.

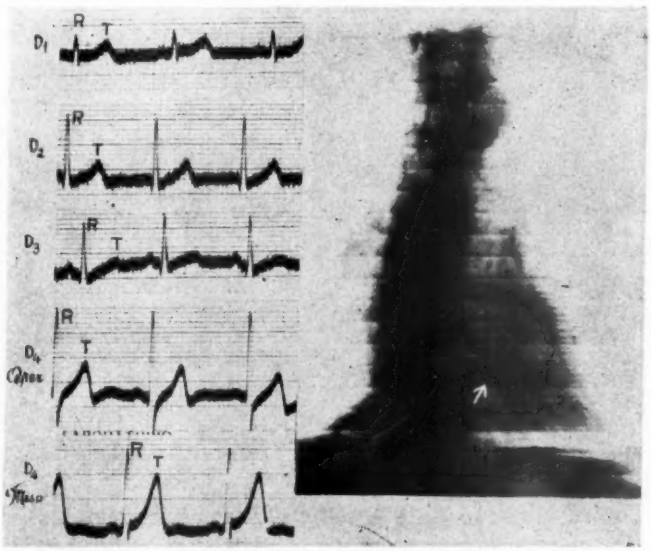


Fig. 12.—Patient with a bullet within the heart (see arrow). The electrocardiogram is normal.

We have mentioned that in angina pectoris electrocardiographic abnormalities may be present only during attacks and that in infarction the electrocardiogram may be normal under a variety of circumstances. Wounds of the heart or a foreign body in the myocardium are somewhat analogous to infarction. In such cases, the electrocardiogram may be normal because the region involved cannot be explored by means of the leads used or because the coronary vessels and the conduction system have escaped damage and the amount of ordinary cardiac muscle destroyed has been small. Fig. 12 illustrates a case in which roentgenographic examination in various planes clearly showed a

bullet lying within the heart shadow; the electrocardiogram was normal in every respect. There were no disturbances of cardiac function.

Arterial hypertension is another cardiovascular disorder in which the electrocardiogram is often normal. In this study, simple left axis deviation has been considered abnormal only when encountered in the electrocardiogram of a subject of definitely asthenic habitus. We have considered a systolic pressure of 150 and a diastolic pressure of 90 the extreme limit of normality. Since one or both of these limits are frequently attained by normal subjects as a consequence of emotion or some other factor which raises the blood pressure temporarily, and because the height of the blood pressure and the pulse pressure are obviously important factors in determining the effect of hypertension upon the heart, we have prepared a table (Table II) showing the incidence of normal electrocardiograms in different groups of cases. It will be seen that we obtained normal electrocardiograms in a relatively large number of our cases of hypertension. This was due in part to the great frequency of

TABLE II. INCIDENCE OF ABNORMAL ELECTROCARDIOGRAMS IN CASES WITH NORMAL AND HIGH BLOOD PRESSURE

BLOOD PRESSURE		ELECTROCARDIOGRAM NORMAL	ELECTRO-CARDIOGRAM ABNORMAL	TOTAL
SYSTOLIC (MM. HG)	DIASTOLIC (MM. HG)			
150	80-90	4	3	7
150	91-100	10	6	16
150	101-115	2	5	7
151-160	85-100	18	12	30
151-160	101-120	3	8	11
151-160	121-135	-	2	2
161-170	91-100	6	9	15
161-170	101-120	3	6	9
161-170	121-135	-	4	4
171-180	80-105	10	6	16
171-180	106-115	7	10	17
171-180	116-130	5	8	13
181-190	85-95	1	3	4
181-190	96-125	4	6	10
181-190	126-140	2	9	11
191-200	100-115	3	6	9
191-200	116-125	3	6	9
191-200	126-150	-	4	4
201-210	100-120	1	3	4
201-210	121-140	2	1	3
201-210	141-155	-	1	1
211-220	100-120	1	3	4
211-220	121-140	2	7	9
211-220	141-165	1	3	4
221-230	120-130	-	4	4
221-230	131-150	-	2	2
221-230	151-160	-	1	1
231-240	110-140	-	2	2
231-240	141-160	-	3	3
231-240	161-180	-	3	3
241-250	130	1	1	2
241-250	160	-	1	1
241-250	170	-	1	1
251-260	150-165	-	3	3
265	150	1	-	1
266-300	140-190	-	3	3
Total		90	155	245

TABLE III. DISTURBANCES OF CARDIAC FUNCTION IN NINETY PATIENTS WITH HYPERTENSION AND NORMAL ELECTROCARDIOGRAMS

MANIFESTATION OF DISTURBED CARDIAC FUNCTION	NUMBER OF CASES
Palpitation, syncope, giddiness, poorly characterized pain	30
Dyspnea of effort	13
Slight congestive failure	8
Moderate congestive failure	2
Marked congestive failure	-
Acute edema	1
Angina of rest	2
Angina of effort	2
No disturbances	32

this disorder and to the large number of cases in which the increase in blood pressure was small. The number of normal electrocardiograms decreased as the blood pressure became higher and the pulse pressure smaller. If it had been possible for us to follow our patients from the onset of the hypertension, we should probably have found that the duration of the disease was an important factor in bringing about electrocardiographic abnormalities.

The incidence of various disturbances of cardiac function in a series of 90 cases of hypertension in which the electrocardiogram was normal is shown in Table III. It will be noted that in 75 of the 90 cases there were no functional disturbances of major significance, that is other than palpitation and dyspnea on effort. An electrocardiographic examination is, therefore, of considerable value in hypertension and may sometimes help, as was pointed out by Wilson[1] in the differentiation of emotional or transient from permanent increases in blood pressure. Since congestive cardiac failure is one of the most frequent and most serious complications of hypertension, any sign which suggests that it is imminent or indicates that extensive cardiac changes are present would be of great value. A moderate increase in the cardiac area has no great significance, and gallop rhythm does not usually occur until late. In the electrocardiogram, the earlier changes consist in the development of unusually large QRS deflections and left axis deviation with T waves of the normal type; in the later stages of hypertensive heart disease T_1 becomes flat and finally negative. (See Fig. 35 of Master's[5] book which shows the gradual development of electrocardiographic changes in a case of hypertension.)

There are, however, cases in which extremely high blood pressure, a low pulse pressure, and pronounced disturbances of cardiac function are associated with an electrocardiogram of the normal type. A case of this kind is illustrated by Fig. 13. In this instance, the systolic pressure varied from 230 to 265. The first electrocardiogram, taken on Oct. 7, 1938, was normal; the second, taken five years later, was also normal, even as regards the ventricular complexes of the precordial leads. The number of cases of this kind is relatively small, and it may be that, as Master[5] believes, simultaneous enlargement of the right and left ventricles is responsible for the failure of electrocardiographic changes to develop. If this is the case, we should expect the prognosis to be less favorable when severe hypertension with a great increase in the cardiac area is accompanied by a normal electrocardiogram.

Electrocardiograms of the normal type are often encountered in other varieties of cardiovascular disease which place a burden upon both ventricles at the same time: in patent ductus arteriosus, in arteriovenous aneurysm, and in aortic insufficiency associated with mitral stenosis or a pulmonary lesion.

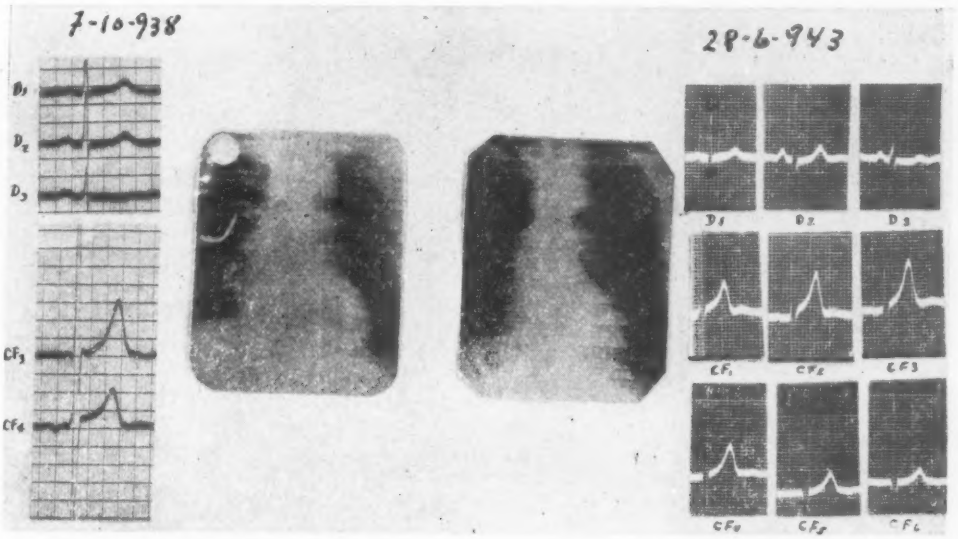


Fig. 13.—Marked essential hypertension of five years' duration. The electrocardiogram and orthodiagram show no significant changes over this period of time.

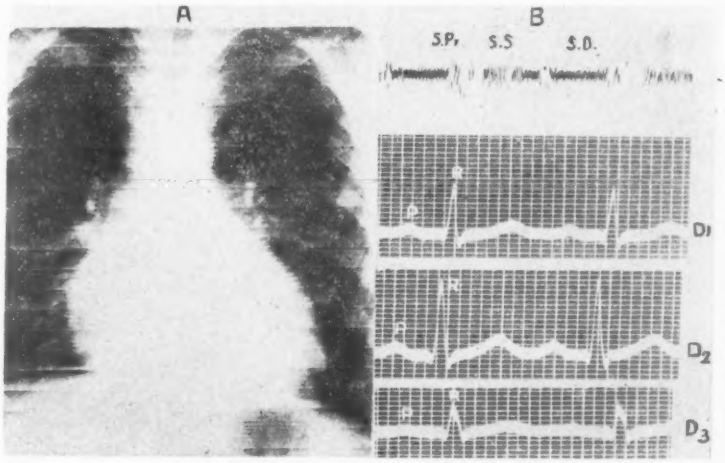
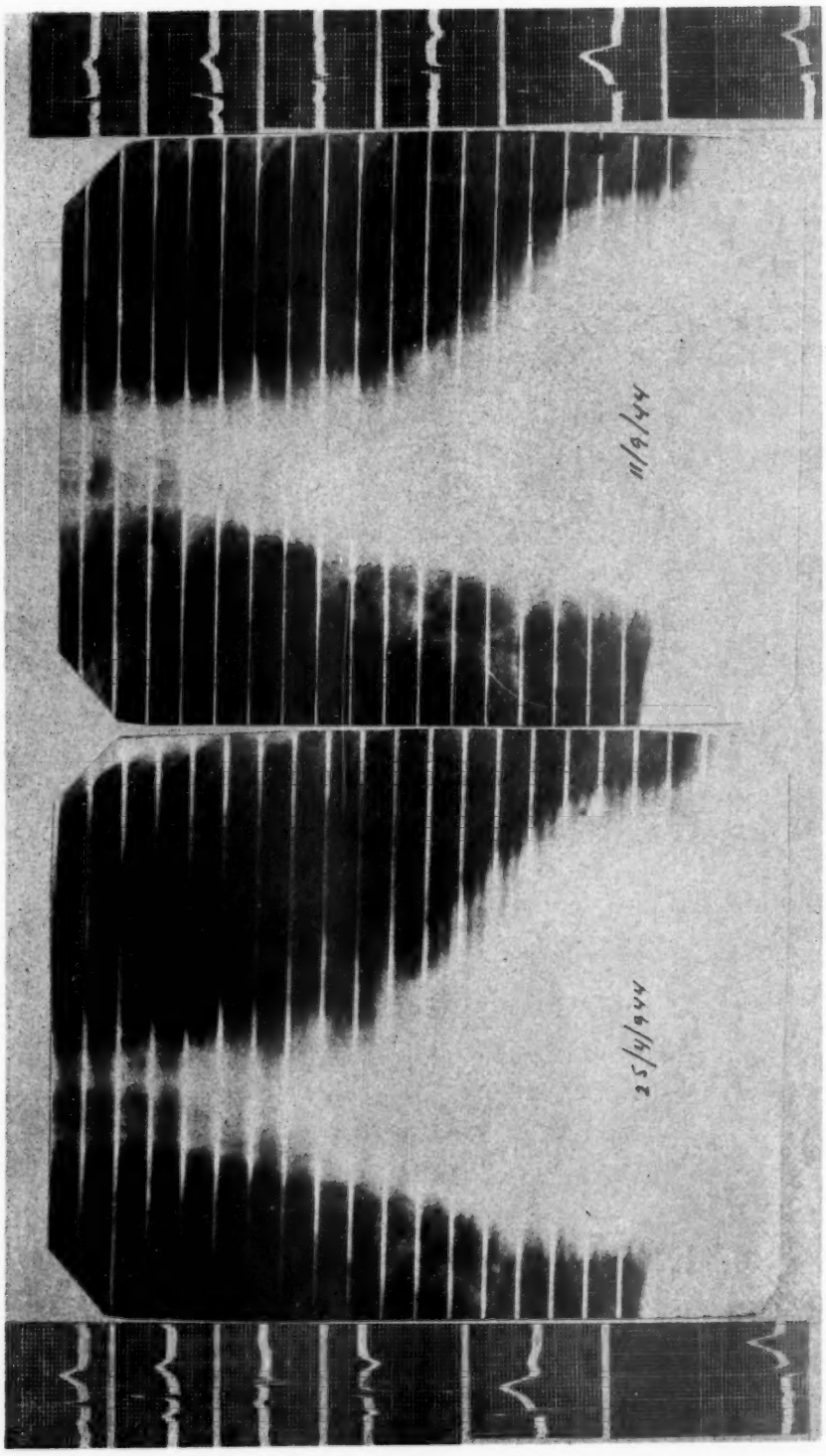


Fig. 14.—Normal electrocardiogram in a patient with mitral stenosis and aortic insufficiency.

The occurrence of a normal electrocardiogram in aortic insufficiency associated with mitral stenosis is illustrated in Fig. 14. Fig. 15 illustrates a case of ateriovenous aneurysm of the femoral artery. The electrocardiogram was normal both before (A) and after the corrective operation (B). Fig. 16 illustrates the occurrence of a normal electrocardiogram in patent ductus arterio-



A. B.

Fig. 15.—Patient with arteriovenous aneurysm of femoral artery. The electrocardiogram was normal both before and after operation.

sus. Simultaneous involvement of both ventricles may, then, be a common cause of the absence of electrocardiographic abnormalities in certain types of heart disease.

It is more difficult to account satisfactorily for the absence of electrocardiographic abnormalities in cases of mitral stenosis with great auricular enlargement. In a great many of the numerous cases in which this valve lesion fails to give rise to recognizable abnormalities of the P wave, we can assume that the obstruction at the mitral orifice is slight or that it has not been of long duration. There are, however, instances in which the disproportion between the size of the P deflection and the amount of auricular enlargement makes it hard to believe that there can be any close relation between them.

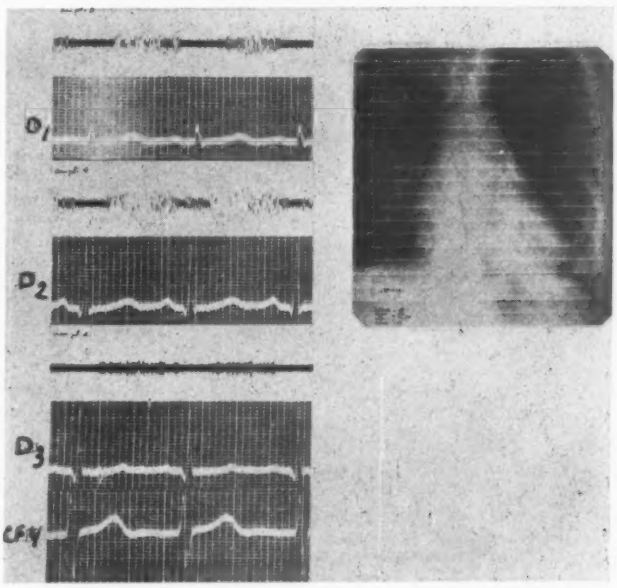


Fig. 16.—Normal electrocardiogram in a patient with a patent ductus arteriosus.

Fig. 17 illustrates a case of mitral stenosis of this kind. It is possible that the deformity of the P wave often seen in mitral stenosis is usually due to auricular myocardial lesions which interfere with the spread of the cardiac impulse. If this were the case, the absence of abnormalities of this deflection in many cases in which there is great auricular enlargement and the presence of such abnormalities in others in which auricular enlargement is less pronounced would be easier to understand. It must, however, be borne in mind that the magnitude of the changes in the P wave may be more closely related to the thickness of the auricular wall than to the size of the auricular shadow in the roentgenogram and that we do not know that the leads in common use are adequate to detect auricular enlargement or hypertrophy under all circumstances; abnormal P waves are frequently present in only one of the limb leads. We do know, however, that abnormally large P waves are sometimes encoun-

tered during emotion or after exertion so that it is clear that changes in the tone of the accessory cardiac nerves also play a part in determining the size of this deflection.

In mitral stenosis, modifications of the P waves are usually accompanied by right axis deviation and, in advanced cases, by inversion of T_2 and T_3. When there is no axis deviation (it is not the rule), the lesion is usually recent, of low grade, or associated with some condition which places a burden upon the left ventricle.

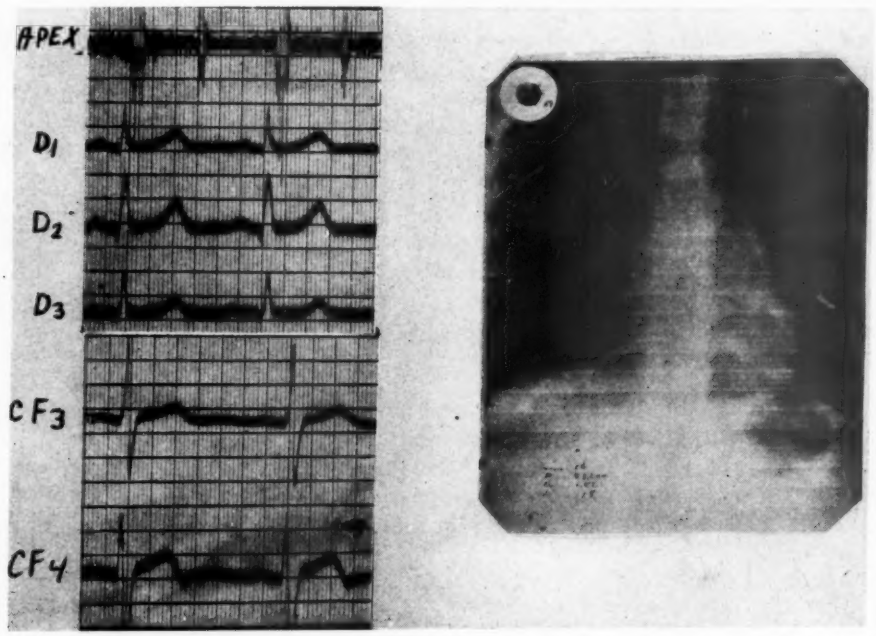


Fig. 17.—Normal electrocardiogram in a patient with mitral stenosis. Roentgenographic examination of heart suggests definite auricular enlargement.

The electrocardiogram was normal in eleven of our twenty-two cases of organic mitral insufficiency. In these cases, the diagnosis was based on the presence of an intense mitral systolic murmur, enlargement of the heart, and a clear history of rheumatic manifestations. It is possible that, in many of the eleven cases in which the electrocardiogram was abnormal, mitral stenosis was present without the characteristic signs or that the myocardium had been damaged by the rheumatic infection that produced the valve lesion.

The electrocardiogram is sometimes normal in rheumatic carditis and in beriberi. Fig. 18 illustrates a case of the latter in which the electrocardiogram was abnormal at first but became normal when the heart was still considerably enlarged (May 1, 1942). The first tracing shows inversion of the T waves in the chest leads. When the final tracing was taken the cardiac area was within normal limits. Fig. 19 illustrates the occurrence of a normal electrocardio-

gram in a case of rheumatic carditis, without auscultatory signs of involvement of the valves, in which the heart was greatly enlarged.

We may now turn our attention to a comparison of the electrocardiographic findings and the evidence of disturbances of the functional capacity of the heart (Table IV). This table shows that a normal electrocardiogram is

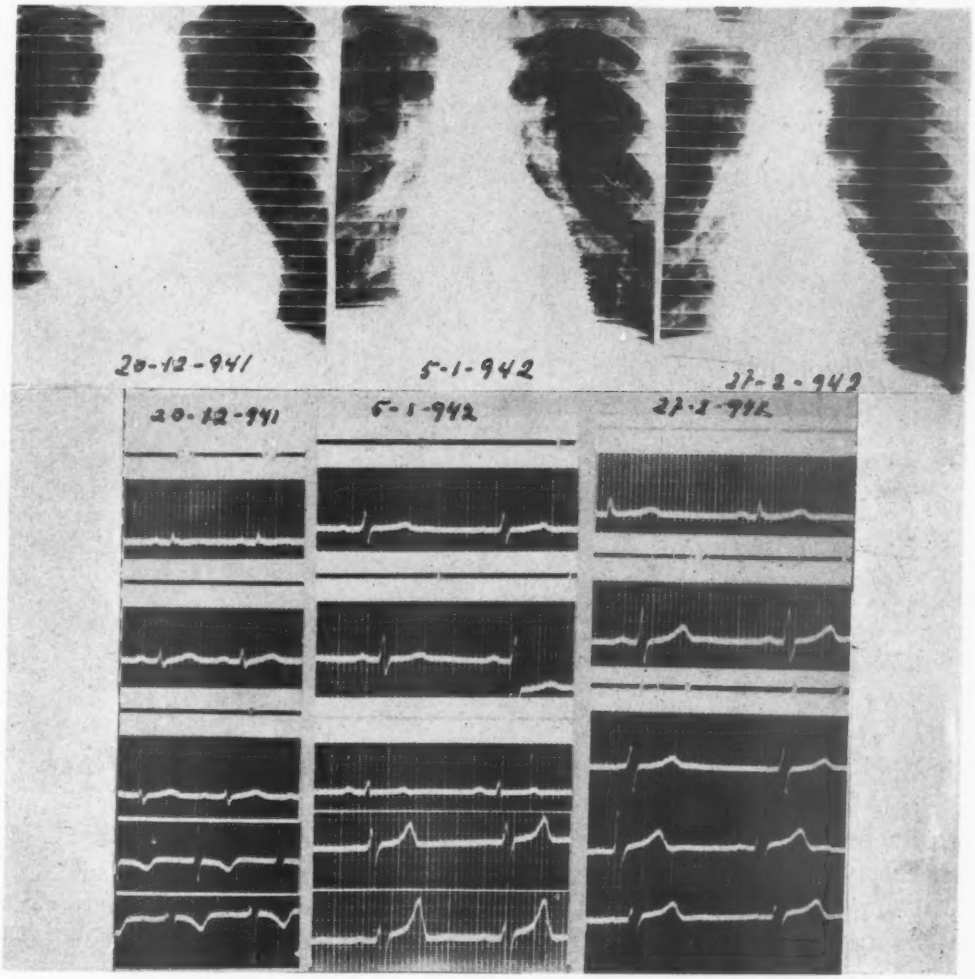


Fig. 18.—Electrocardiograms and roentgenographic examinations of the heart in a patient with beriberi.

very frequently obtained when the functional capacity of the heart is good (I and II) and when symptoms are absent or insignificant. It is also normal in a great many cases in which the chief symptom is dyspnea on exertion, which often develops long before there are objective signs of cardiac weakness. A fairly large number of the cases placed in Group IV (slight congestive failure with more marked dyspnea and râles at the lung bases) showed normal electro-

TABLE IV. DISTURBANCES OF CARDIAC FUNCTION IN 234 PATIENTS WITH CARDIOVASCULAR DISEASE AND NORMAL ELECTROCARDIOGRAMS

GROUP NUMBER	EVIDENCE OF FUNCTIONAL DISTURBANCE	NUMBER OF CASES
I	None	108
II	Vague pain, giddiness, palpitation	72
III	Dyspnea on effort	21
IV	Slight congestive heart failure	16
V	Angina of rest	4
VI	Angina of effort	10
VII	Acute pulmonary edema	1
VIII	Cardiac asthma	1
IX	Marked congestive heart failure	1

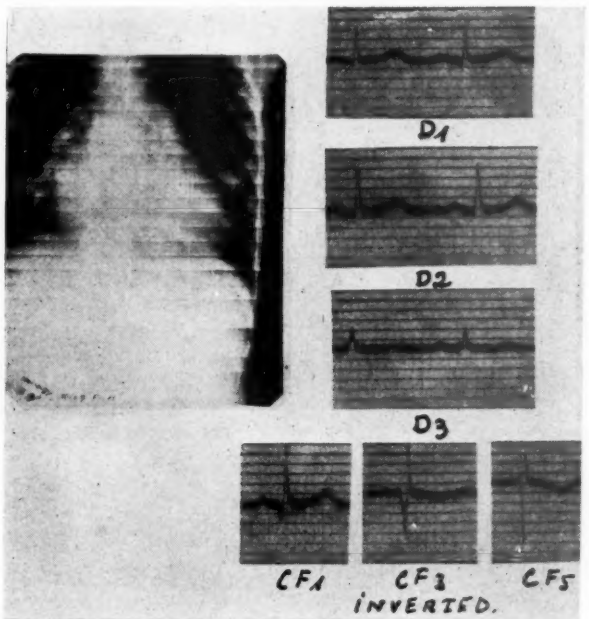


Fig. 19.—Patient with rheumatic carditis and roentgenographic evidence of cardiac enlargement. The electrocardiogram is normal.

cardiograms. Patients of the kind in question may go on for years without becoming totally incapacitated, particularly when hypertension is the cause of the cardiac abnormality. It is possible that a normal electrocardiogram in cases of this sort indicates that the prognosis is more favorable, but the data in our possession do not permit any final conclusion on this point. In the case of angina pectoris, it is well known that the electrocardiogram is often normal apart from the transient modifications which may occur during attacks. We may suppose that when this is the case the coronary circulation is adequate when the patient is at rest.

There was one case of acute pulmonary edema in which the electrocardiogram was normal. The relief that some patients with this disorder experience after the administration of nitroglycerin suggests that it may sometimes be initiated by acute coronary insufficiency. Such a mechanism would help to

explain, as in the case of angina pectoris, the occurrence of alarming symptoms in a person who feels quite well between the attacks and presents a normal electrocardiogram. In cardiac asthma (VIII) some factor of a like kind may occasionally exist, for this condition sometimes develops in patients who are otherwise in relatively good condition and the injection of adrenalin frequently gives prompt relief. We had only one case in which cardiac asthma was associated with hypertension. In many instances, this symptom appears to be an allergic phenomenon superimposed upon slight passive congestion of the lungs.

The single case placed in Group IX (high-grade cardiac failure) was a particularly interesting one. The patient presented the characteristic picture of beriberi probably induced by a very poor nutritional state due to peptic ulcer complicated by incessant vomiting. Physical examination showed pronounced edema of the lower extremities, great enlargement of the heart, and muffled heart sounds. The administration of vitamin B was followed by a diuresis of 6 liters during the following twenty-four hours. The size of the heart rapidly decreased and returned to normal. The electrocardiogram was abnormal at first but became normal while the heart was still much enlarged. Two months after treatment was begun an operation for peptic ulcer was performed and the patient made a good recovery. With this exception, we have not encountered a normal electrocardiogram in the presence of high-grade cardiac failure, but this may well be because the majority of our patients had already received enough digitalis before the first electrocardiogram was taken to induce modifications of the T complex. The question also arises as to whether modifications of the RS-T segment and the T wave in cardiac failure may not often be due to the associated anoxia.

SUMMARY

In a series of 722 cases of cardiovascular disease, the electrocardiogram was of the normal type in 223 instances.

1. The electrocardiogram is often normal in those diseases, such as syphilitic aortitis, arteriosclerosis, hypertension, and pericarditis, which damage the myocardium secondarily or late in their course.

2. In certain cardiovascular disorders, such as angina pectoris, the electrocardiogram may be abnormal during a crisis, but is normal in a large percentage of the cases if it is taken when the patient is free of symptoms.

3. The electrocardiogram may be normal when the cardiac lesion is localized and does not involve the conduction system or the coronary arteries. This may happen in the case of tumors, abscesses, or foreign bodies.

4. Cardiac abnormalities that place a burden upon both ventricles simultaneously, such as patent ductus arteriosus, arteriovenous aneurysm, aortic insufficiency plus mitral stenosis, or mitral stenosis complicated by hypertension, are less likely to modify the electrocardiogram than those that increase the work of the right or of the left ventricle alone.

5. Auricular enlargement demonstrable by roentgenographic examination frequently fails to produce recognizable abnormalities of the auricular complex.

6. A normal electrocardiogram is rarely obtained when high-grade cardiac failure is present, possibly because many patients with this condition have received sufficient digitalis to modify the T wave before the electrocardiogram is taken or because the associated anoxia tends to alter the T complex.

7. The electrocardiogram is not infrequently normal in cases of acute pulmonary edema and in cases of cardiac asthma. It is suggested that this may be because these crises are precipitated by transient factors. We are referring here to routine electrocardiograms not taken during attacks.

8. By the use of additional leads and by taking tracings during crises in those conditions in which these occur, it is probable that the number of cases of heart disease in which the electrocardiogram is normal might be considerably reduced.

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CERTAIN EFFECTS OF POSITIVE PRESSURE RESPIRATION ON THE CIRCULATORY AND RESPIRATORY SYSTEMS

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ALTERATION of the pressure within the respiratory tract has been used in attempts to resuscitate the dead or near dead,[1-3] in maintenance of respiration during thoracic operations,[4, 5] and in the treatment of acute pulmonary edema.[6-8] During the nineteenth century it was used in the treatment of chronic respiratory disease,[9-11] but it was found to be of little or no value and is no longer used.

During World War II an increase in the respiratory pressure has been used to maintain adequate respiration during high altitude flying (40,000 to 50,000 feet [12,000 to 15,000 meters]) because at this altitude the partial pressure of alveolar oxygen drops so low that, although the pilot breathes 100 per cent oxygen, adequate oxygenation of the arterial blood is not maintained. To increase the partial pressure of the alveolar oxygen, the pilot wears a tight fitting mask and the oxygen is administered under positive pressure. To be effective, this pressure has to be higher than that which has been used for other purposes. Therefore, it seemed wise to study in dogs the effects of this higher positive respiratory pressure before it was put into widespread use by human beings.*

These investigations were made with two instruments;† the first instrument, to be called *the continuous pressure regulator,* was adjustable and could be regulated to deliver a positive pressure of up to 25 cm. of water, zero being the prevailing atmospheric pressure. This positive pressure was continuous throughout the respiratory cycle although there was a slight fluctuation in the pressure due to respiration. Breathing through this instrument will be called *continuous positive pressure respiration.* The study of continuous positive pressure respiration was largely limited to a pressure of 20 cm. of water.

The second instrument, known as the *intermittent pressure demand regulator,* was an ingenious device with a diaphragm and a spring loaded valve designed so that, although during inspiration a positive pressure of 20 cm. of water was delivered, the very beginning of expiration closed the inlet valve and the rest of expiration took place at a much lower pressure. The expiratory

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†Furnished by the Commanding General, Material Command, Engineering Division, Aero Medical Laboratory, Wright Field, Dayton, Ohio.

valve was adjustable so that the major part of expiration could take place at from 5 to 12.5 cm. of water pressure. During these experiments the valve was set so that most of expiration was at a pressure of 6.25 cm. of water. Toward the end of the expiratory phase of respiration, the pressure fell to 2.5 cm. of water and remained at this pressure until the beginning of the next inspiration lowered the pressure to less than 2.5 centimeters. This allowed the inlet valve to open and the pressure to rise to 20 cm. of water again. Breathing through this instrument will hereafter be called *intermittent positive pressure respiration.*

I. THE EFFECTS OF POSITIVE PRESSURE RESPIRATION ON THE RESPIRATION AND THE CIRCULATION OF NORMAL DOGS

Methods.—After anesthetization with pentobarbital sodium, given intravenously in doses of 25 to 30 mg. per kilogram of body weight, the dogs were placed in a special dog rack on their backs. Arterial blood pressure was measured by a mercury manometer connected to a cannulated femoral or carotid artery. The venous blood pressure was measured by a water manometer connected to a large needle inserted into the right or left external jugular vein. A solution of heparin was used as the anticoagulant for these manometers. The rate of respiration was recorded by a pneumograph, and the heart rate was counted at frequent intervals.

The positive respiratory pressure was administered through an intratracheal cannula, the distal end of which was surrounded by a rubber tampon which, when inflated, prevented the escape of gas around the cannula. The respiratory pressure was supplied by tanks of compressed gas (helium, 80 per cent, and oxygen, 20 per cent) and controlled by the regulators described previously. This mixture of gases was used because of its low density, approximately one-third that of air. Using a gas of such low density reduced to a minimum the effects of breathing through the slightly narrowed orifices of the intratracheal cannula and the pressure regulator.

The respiratory dead space was kept to a minimum. Even so, it consisted of the intratracheal cannula, a glass T tube, a water manometer to register the respiratory pressure, the pressure regulator, and short lengths of rubber tubing to connect them. After a control period of observation with the respiratory pressure normal, the positive pressure was administered for a period of three hours, after which the respiratory pressure was reduced to normal.

As described subsequently in the study of continuous positive pressure respiration, suddenly raising the respiratory pressure from normal to 20 cm. of water pressure always resulted in apnea. Therefore, when studying this type of pressure breathing, the pressure usually was raised from normal to 10 cm. and then to 15 cm. for five minute periods, after which it was raised to 20 cm. for the rest of the experiment.

Continuous Positive Pressure Respiration.—The effect of continuous positive pressure respiration was studied on four animals (Table I). Only one of the four tolerated the planned period of three hours of pressure breathing. In

TABLE I. THE EFFECT OF CONTINUOUS POSITIVE PRESSURE RESPIRATION*

	ANIMAL			
	21	31	36	35
Respiratory rate per minute	12 to 6	14 to 9	10 to 4	9 to 5
Heart rate per minute		128 to 140	186 to 150	140 to 152
Arterial pressure, mm. Hg	130 to 150	100 to 105	115 to 150	100 to 50
Venous pressure, mm. water	51 to 146	0 to 102	64 to 140	32 to 108

*The first figure in each column is the measurement taken just before beginning pressure breathing, and the second figure is the measurement after the respiratory pressure had been raised to 20 cm. of water.

the other three apnea developed after five, seven, and ten minutes, respectively. The first two died; the third was saved by discontinuing the positive respiratory pressure. (However, this high percentage of deaths from apnea did not occur in a later series of experiments. When a group of five animals was given three hours of continuous positive pressure respiration with a pressure of 20 cm. of water there was only one death, which occurred after forty-seven minutes of pressure breathing.)

In all four animals the respiratory rate decreased when continuous positive pressure respiration was begun, the average rate decreased from 11 to 6 per minute. When the continuous positive respiratory pressure was discontinued after three hours the respiratory rate of the surviving animal increased from 10 to 34 per minute. The initiation of continuous positive pressure respiration was followed by increases in the venous pressure varying from 76 to 102 mm. of water, with an average increase of 87 millimeters. Neither the heart rate nor the arterial blood pressure was so consistently affected: there were increases in some animals and decreases in others.

The occurrence of apnea, which prevented three of the four animals from completing the three hours of continuous positive pressure respiration, was studied in a separate group of experiments (Table II). It was found that raising the respiratory pressure from normal to 10 cm. of water would seldom cause apnea but that raising it from normal to 20 cm. of water would always cause apnea. This apnea usually occurred with the thorax of the animal held in the expiratory position and varied in length from a few seconds to several minutes, sometimes resulting in the death of the animal. Repeated trials showed no tendency toward accommodation to the pressure and shortening of the period of apnea, but it was noted that inadequate anesthesia would

TABLE II. THE EFFECT OF ATROPINIZATION AND BILATERAL VAGOTOMY ON THE APNEA CAUSED BY A CONTINUOUS POSITIVE RESPIRATORY PRESSURE OF 20 CM. OF WATER

	ANIMAL			
	46	12	21	11
	DOSE OF ATROPINE SULFATE (MG. PER KG. OF BODY WEIGHT, INTRAVENOUSLY)			
	0.1	0.01	0.1	0.2
	AVERAGE LENGTH OF APNEA (SECONDS)			
Before atropinization	20	64	93	62
After atropinization	20	82	77	54
After bilateral vagotomy	0	0	0	0

result in shorter periods of apnea. The intravenous administration of atropine sulfate in doses up to 0.2 mg. per kilogram of body weight had little or no effect on the length of the period of apnea. After bilateral vagotomy there was never any period of apnea when the respiratory pressure was raised from normal to 20 cm. of water.

Intermittent Positive Pressure Respiration.—The effect of intermittent positive pressure respiration was studied on five animals over a period of three hours. All survived with no untoward results (Table III, Fig. 1).

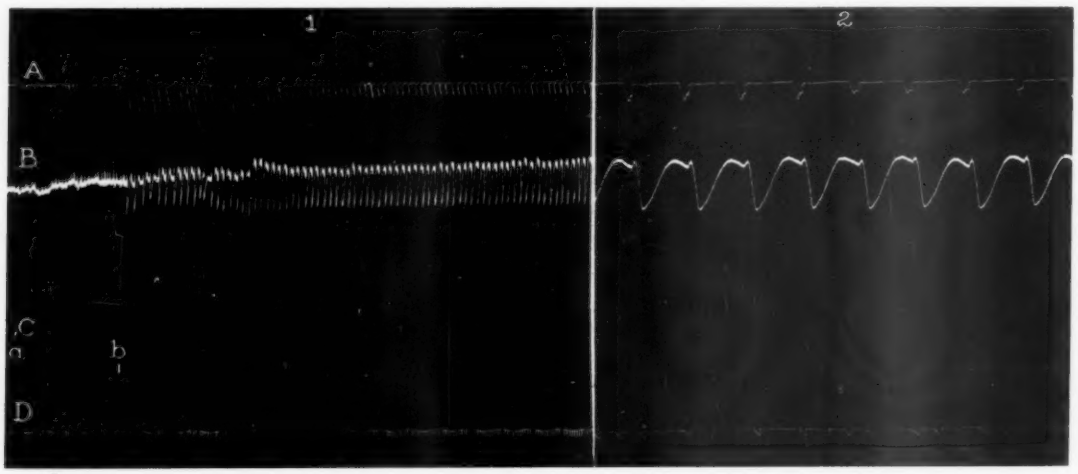

Fig. 1.—Effect of an intermittent positive respiratory pressure of 20 cm. of water on the respiration and the carotid arterial blood pressure. *A* is the respiratory rate recorded by a thoracic pneumograph. *B* is the carotid arterial blood pressure recorded by a mercury manometer with a writing lever. *C* is the zero line for the blood pressure. *D* is the time in five-second intervals. At *a* the respiratory pressure was normal. At *b* intermittent positive pressure respiration was begun. Between the two portions of the tracing the kymograph was speeded up from 12 to 111 mm. per minute.

TABLE III. THE EFFECT OF INTERMITTENT POSITIVE PRESSURE RESPIRATION*

	ANIMAL														
	22			38			39			40			24		
Respiratory rate per minute	20	to	5	16	to	6	18	to	20	20	to	18	13	to	20
Heart rate per minute	180	to	174	200	to	196	144	to	180	200	to	200	192	to	200
Arterial pressure, mm. Hg	140	to	130	105	to	100	105	to	90	130	to	125	125	to	110
Venous pressure, mm. water	−6	to	102	6	to	89				22	to	64			

*The first figure in each column is the measurement taken just before beginning pressure breathing, and the second figure is the measurement shortly afterward.

The respiratory rate was usually slowed when intermittent positive pressure respiration was begun; the average rate for the five animals dropped from 17 to 14 per minute. When the positive pressure was discontinued at the end of the three-hour period, the respiratory rate increased; the average changed from 11 to 28 per minute.

After intermittent positive pressure respiration had begun there was a marked fluctuation in the arterial blood pressure during the respiratory cycle. During expiration, when the respiratory pressure was low, the arterial blood pressure was at approximately the same level as when the animal was breath-

ing at a normal respiratory pressure. On inspiration, when the respiratory pressure rose to 20 cm. of water, there was first a slight rise in the blood pressure, then a rapid decrease of as much as 50 to 60 mm. of mercury. When expiration began and the pressure in the respiratory tract fell, there was first a slight further drop in the blood pressure and then a rapid increase up to the control level, where it remained until the next inspiration began, whereupon the cycle would be repeated.

The venous blood pressure was affected in a reverse manner. That is, the venous pressure increased during the inspiratory phase of respiration but decreased on expiration, the maximal venous pressure was as much as 100 to 110 mm. of water and the fluctuation amounted to 70 to 80 millimeters. The fluctuation of the venous pressure was so rapid that the inertia of the column of water in the manometer and tubing caused a lag, which prevented an accurate indication of the venous pressure, even though in most of the experiments the manometer was connected to a 13-gauge needle inserted into an external jugular vein. The heart rate was not consistently affected by intermittent positive pressure respiration.

Intermittent positive pressure respiration never caused apnea. In fact, it could not cause it, as the intermittent pressure demand regulator was designed to function as a resuscitator, and, if spontaneous respiration had ceased, the instrument would have automatically ventilated the lungs at a slow rate.

The Pulmonary Arterial Pressure, the Pulmonary Venous Pressure, and the Pleural Pressure.—These were measured in two animals. After a preliminary trial with both types of positive pressure respiration, right thoracotomy was done and cannulas were inserted into branches of the pulmonary artery and vein. The cannulas were connected to rubber tubing, which was brought out through the incision and connected to manometers: the arterial cannula was connected to a mercury manometer with a writing lever to record the pressure on a kymograph, and the venous cannula was connected to a water manometer from which the pressure was read and recorded. A glass T tube was placed in the thorax with its single arm passing out through the incision and connected to a water manometer to measure the pleural pressure. The thoracotomy incision was then closed tightly, the lungs being almost completely expanded just before the closure was completed.

After the animal had recovered from the immediate effects of the operation the effect of both types of pressure breathing was studied (Table IV). The effect was essentially the same in both animals. Continuous positive pressure respiration caused an elevation of the pulmonary venous pressure and the pulmonary arterial pressure, which was proportional to the respiratory pressure. Intermittent positive pressure respiration caused an elevation of both the pulmonary arterial and venous pressures, but the elevation was less than that caused by a continuous positive respiratory pressure of 20 cm. of water. The pleural pressures were elevated by both types of pressure breathing but the pressures were still quite low in the inspiratory phase of respiration, which suggested that the respiratory gas did not flow in through the regulator and the tracheal cannula as fast as the animal expanded its thorax.

TABLE IV. THE EFFECT OF POSITIVE PRESSURE RESPIRATION ON THE ARTERIAL AND VENOUS PRESSURES OF THE GREATER AND LESSER CIRCULATIONS OF ANIMAL 52

	FEMORAL ARTERIAL PRESSURE (MM. HG)	JUGULAR VENOUS PRESSURE (MM. H_2O)	PULMONARY ARTERIAL PRESSURE (MM. HG)	PULMONARY VENOUS PRESSURE (MM. H_2O)	PLEURAL PRESSURE (CM. H_2O)	
					INSPIRATION	EXPIRATION
Normal pressure respiration	100	−3	30	44	−10	+5
Continuous positive pressure respiration (10.16 cm.)	118	15	36	88	−6	+12
Continuous positive pressure respiration (15.24 cm.)	108	65	37	114	−2	+16
Continuous positive pressure respiration (20.32 cm.)	99	100	39	144	0	+20
Normal pressure respiration	99		35			
Intermittent positive pressure respiration	96	10	37	60	−3	+11

Comment: Although the physiologic effects of continuous and intermittent positive pressure respiration differ in some respects, it seems wise to discuss them together so that comparisons and contrasts of the results can be made more easily.

Both types of pressure breathing had a significant effect on the respiratory rate. In almost every case the initiation of positive pressure respiration of either type caused a slower and deeper respiration than had been present during the control observation period. In these experiments the respiratory rate was recorded by a thoracic pneumograph with a kymograph and writing lever. With this instrument the respiratory rate can be measured easily and accurately, but the volume of each inspiration can be estimated only crudely by the length of the excursions of the writing lever. Consequently no data can be given regarding the difference in the volume of inspirations during normal respiration and pressure breathing, except that it was increased during the latter. Roentgenographically it was seen that the diaphragm was depressed during both types of positive pressure respiration.

Inhibition of respiration by a continuous positive respiratory pressure has been reported by many different workers.[12, 13] On the other hand, Boothby and Berry[14] reported that a positive pressure of as much as 15 cm. of water did not produce apnea in either human beings or dogs. The difference in results may have been due to the state of consciousness, since Boothby and Berry worked with unanesthetized subjects whereas the other investigators used anesthetized animals. Another factor may have been the amount of respiratory dead space, since Boothby and Berry used apparatus that reduced the dead space to a very small amount. In our experiments it was noted that if the animals' anesthesia became light there would be a considerable shortening of the period of apnea. This apnea is undoubtedly influenced by afferent impulses passing up the vagus nerves, because, after bilateral vagotomy, a continuous

positive respiratory pressure of 20 cm. of water never caused apnea. Adrian[15] has made a careful study of the action currents passing up the vagus nerve during inflation of the lung and has shown that their frequency is proportional to the degree of distention of the lung. He further showed that adaptation to the stimulus took place very slowly: the frequency of the action current decreased very little during a period of thirty seconds. This slow adaptation to the stimulus undoubtedly contributes to the prolonged period of apnea that occurs when a continuous positive respiratory pressure of 20 cm. of water is instituted.

There was no consistent change in the heart rate when either type of positive pressure respiration was initiated. Sometimes there was an increase; at other times the rate stayed the same or decreased.

The effects of the two types of pressure breathing on the arterial blood pressure were quite different. Continuous positive pressure respiration at 20 cm. of water pressure had a variable effect; most frequently there was a slight increase but often there was no change and occasionally there was a decrease. In contrast, intermittent positive pressure respiration had a characteristic and consistent effect on the arterial blood pressure. During the pause between expiration and the next inspiration, when the pressure in the respiratory tract was almost normal, the arterial blood pressure was the same as it had been when the animal was breathing at normal respiratory pressure. When inspiration began and the respiratory pressure rose to 20 cm. of water, there was first a slight increase of arterial pressure, usually lasting three heartbeats, and then there was a marked fall of arterial blood pressure, sometimes as much as 50 or 60 mm. of mercury. Next, as expiration began and the respiratory pressure fell, there was first a further decrease of the arterial pressure, to be followed by a rapid rise up to the level it had been before inspiration began. Then the cycle would be repeated.

The effect of intermittent positive pressure respiration on arterial blood pressure may be explained at least in part as follows: When the pressure in the lungs is raised in inspiration the blood in the pulmonary vascular bed is pushed onward into the left side of the heart, resulting in a momentary increase of the volume of blood flowing into that side of the heart and consequently an increased cardiac output and an elevated arterial blood pressure. However, this increased intrathoracic pressure compresses the right side of the heart and venae cavae and prevents the normal flow of blood from the peripheral veins into the right side of the heart. This results in a decreased output of blood from the right side of the heart and consequently a decreased flow of blood into the left side of the heart. As a result, the output of the left side of the heart decreases and the arterial blood pressure falls. When expiration begins and the respiratory pressure falls, the compression of the pulmonary vascular bed ceases and it fills with blood, thus momentarily decreasing still further the flow of blood into the left side of the heart, resulting in a further decrease of the arterial pressure. Then with a free flow of blood into the right side of the heart and an open pulmonary vascular bed, an increased amount of blood passes through to the

left side of the heart, its output increases, and the arterial pressure returns to normal. As soon as inspiration begins again, the respiratory pressure rises and the cycle is repeated.

The jugular venous pressure was greatly increased by both types of positive pressure respiration. In this respect these experiments confirm the findings of many previous workers.[16, 17, 18] During continuous positive pressure respiration there was a constant elevation of the venous pressure; the rise was proportional to the respiratory pressure. There was a slight fluctuation in the venous pressure with the respiratory cycle, inspiration being accompanied by a slight fall and expiration raising the venous pressure to its maximal level. During intermittent positive pressure respiration there was a marked fluctuation of the venous pressure with each respiratory cycle. Although a 13-gauge needle was usually used there was sufficient resistance in the needle and inertia in the column of fluid so that a complete fluctuation could not take place during each respiratory cycle. Maximal readings were obtained by raising the column of fluid and allowing it to fall at the right moment to coincide with the maximal venous pressure. In this way, it was shown that the venous pressure was raised as much as 100 mm. of water above normal during inspiration.

This elevation of venous pressure was shown to be due to the effect of the increased intrathoracic pressure on the heart and vena cava by opening the thorax widely and preventing the pulmonary pressure from being transmitted to the heart and vena cava. When this was done, intermittent positive pressure respiration caused no increase in the jugular venous pressure. This had been shown previously in experiments by Humphreys, Moore, and Barkley.[19]

The elevation of venous pressure takes place in the lower half of the body as well as in the upper portion. In one experiment, the pressure in the left renal vein was measured and found to be elevated in exactly the same manner as the jugular venous pressure.

This elevation of the peripheral venous pressure is one of the most important effects of pressure breathing on the circulation. Inasmuch as a positive respiratory pressure impedes the flow of blood into the right side of the heart, there is backing up of blood in the peripheral vascular bed with an elevation of the venous pressure as long as the blood volume and the venous tone are maintained. While these are kept up, there is sufficient flow of blood into the right side of the heart to maintain an adequate cardiac output, although it is much below normal according to Huggett[20] and to Humphreys, Moore, Maier, and Apgar.[21] However, if the blood volume is decreased by hemorrhage or trauma, or if the venous tone is lost, there is probably a considerable further decrease of the flow of blood into the right side of the heart and the animal dies of an inadequate cardiac output. Hence, it is of prime importance to maintain an adequate blood volume during pressure breathing, replacing any lost blood as soon as possible or discontinuing the positive respiratory pressure as soon as adequate respiration can be maintained without it.

Pressure breathing of both types had the same effect on the pulmonary venous pressure as it had on the jugular venous pressure. This was probably

brought about in the same manner, as when the thorax was opened widely so that the respiratory pressure was not transmitted to the heart, there was no elevation of the pulmonary venous pressure during intermittent positive pressure respiration.

The pulmonary arterial pressure was increased by both types of pressure breathing, confirming the previous reports of Humphreys, Moore, and Barkley and of Sharpey-Schafer and Bain. The former workers also demonstrated that the pulmonary arterial pulse pressure was decreased by pressure breathing. Continuous positive pressure respiration raised the pulmonary arterial pressure slightly higher than intermittent positive pressure respiration did, and the pulmonary arterial pressure was maintained at a higher level throughout the respiratory cycle. The elevation in either case did not exceed 9 mm. Hg and was proportional to the respiratory pressure. This was to be expected, as the compression of the pulmonary vascular bed was undoubtedly the major cause of the increase of the pulmonary arterial pressure and this must be proportional to the respiratory pressure.

II. THE EFFECTS OF POSITIVE PRESSURE RESPIRATION ON THE SIZE OF THE TRACHEOBRONCHIAL TREE, THE HEART, AND THE INFERIOR VENA CAVA OF NORMAL DOGS

Tracheobronchial Tree.—Method: Three animals were anesthetized with pentobarbital sodium and sufficient barium sulfate powder was blown into the respiratory tract to render the walls of the tracheobronchial tree opaque to roeentgen rays. Right lateral roentgenograms of the thorax were then taken at full inspiration and expiration while the animal was breathing at normal respiratory pressures and at both a continuous and an intermittent positive respiratory pressure of 20 cm. of water. Special care was taken to see that the animal was not moved during the experiment and that the same relationship between the x-ray tube, the animal, and the film cassettes was maintained so that identical films could be obtained. An attempt was made to get roentgenograms at the moment of maximal inspiration and expiration. The slowing of the respiration by the pentobarbital sodium and the pressure breathing facilitated this, but it was not always possible to take the roentgenogram at exactly the right moment. The bronchograms obtained under these conditions were then compared, measurements being made of identical bronchi in each film.

Results: The positive respiratory pressures, both continuous and intermittent, caused an increase of the diameters of the branches of the tracheobronchial tree. This was true of all the branches that could be accurately measured (Table V, Fig. 2).

Comment: Barach and Swenson[22] have reported that a continuous positive respiratory pressure of 5 to 8 cm. of water produced a dilatation of the small bronchi of patients who had chronic bronchial asthma. Our experiments also show that the tracheobronchial tree is dilated during pressure breathing, the dilatation being proportional to the respiratory pressure. Thus, in continuous positive pressure respiration with a pressure of 20 cm. of water, the bronchi are dilated continuously, whereas during intermittent positive pressure respira-

TABLE V. THE EFFECT OF POSITIVE PRESSURE RESPIRATION ON THE DIAMETERS (IN MILLIMETERS) OF THE BRANCHES OF THE TRACHEOBRONCHIAL TREE OF ANIMAL 54

		TRACHEA	RIGHT MAIN BRONCHUS	SECONDARY BRONCHUS	TERTIARY BRONCHUS
Normal pressure respiration	Inspiration	8.5	7.5	3.5	2.5
	Expiration	8.5	7.5	3.5	2.5
Continuous positive pressure respiration	Inspiration	14.0	11.5	6.0	4.0
	Expiration	13.0	10.0	6.0	4.0
Intermittent positive pressure respiration	Inspiration	10.5	9.0	4.5	3.0
	Expiration	10.0	8.0	3.5	3.0

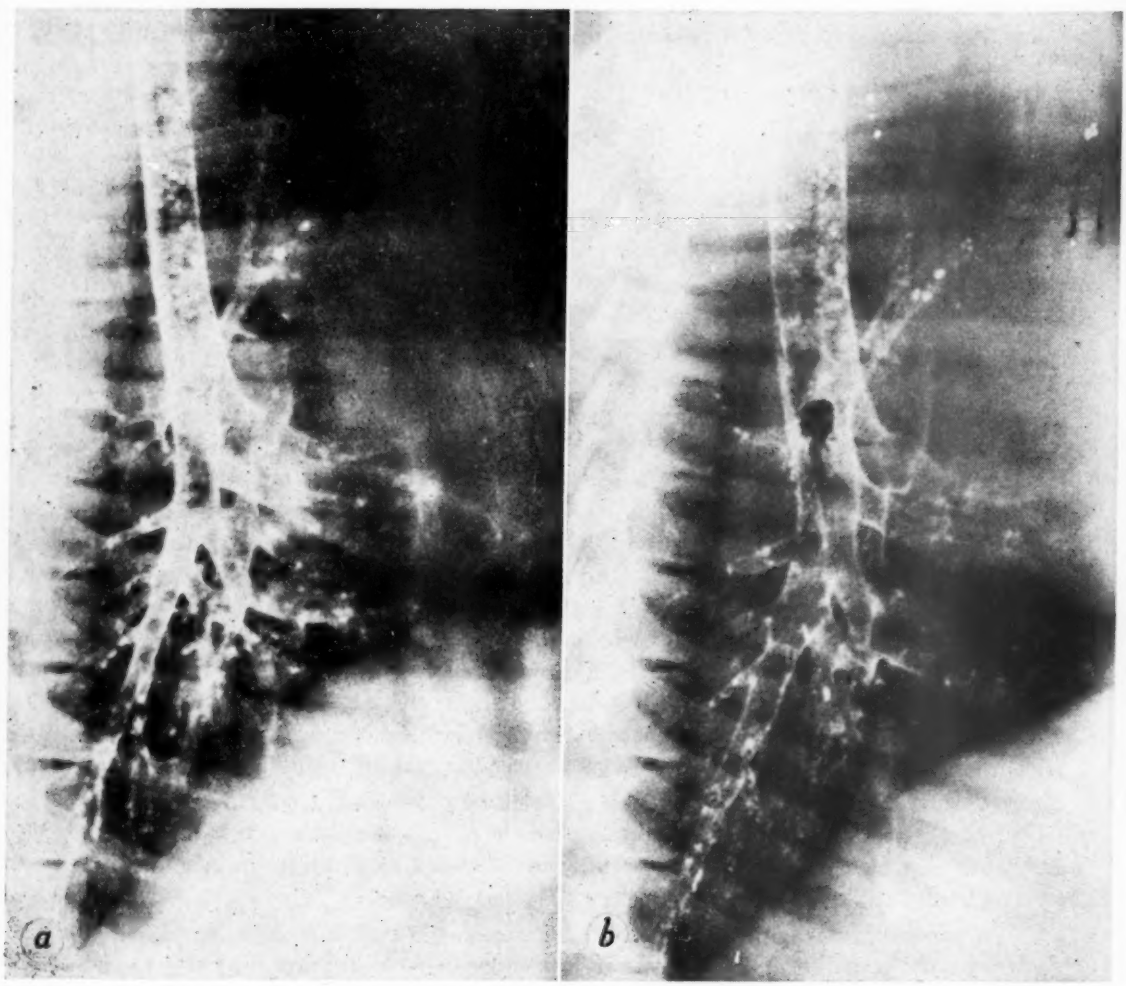

Fig. 2.—Bronchograms showing the effect of a continuous positive respiratory pressure of 20 cm. of water on the size of the tracheobronchial tree. *a* is a lateral view taken at maximal expiration while the animal was breathing at normal respiratory pressure. *b* is a lateral view taken at maximal expiration while the animal was breathing at a continuous positive respiratory pressure of 20 cm. of water.

tion there is very slight dilatation during expiration, when the respiratory pressure is low. This dilatation of the bronchi is probably of minor significance in the application of pressure breathing to aviation but it may be of importance in clinical medicine; for instance, in the treatment of bronchial asthma and in any other disease in which tracheal or bronchial obstruction is interfering with the ventilation of the lungs.

The Heart and Inferior Vena Cava.—Method: The inferior venae cavae of four animals were rendered radiopaque by the injection of thorium dioxide sol into the surrounding tissues through a right thoracotomy incision. After the animals had completely recovered from the operation they were studied roentgenographically to determine the effect of pressure breathing on the heart and the inferior vena cava.

They were anesthetized with pentobarbital sodium and placed in a special rack on the x-ray table to maintain the same relationship between the x-ray tube, the animal, and the film cassette. Anteroposterior roentgenograms of the thorax were obtained at the moment of maximal inspiration and expiration while the animal was breathing at normal respiratory pressure, at a continuous positive respiratory pressure of 20 cm. of water, and at an intermittent positive respiratory pressure of 20 cm. of water. Then the same procedure was repeated with the animal in the left lateral position.

The diameter of the inferior vena cava was measured at a point halfway between the diaphragm and the junction of the vena cava with the heart. The size of the heart was measured in its maximal diameter.

Results: The cardiac shadow was usually slightly smaller on both the lateral and the anteroposterior roentgenogram during pressure breathing of either type than during normal respiration.

In the lateral roentgenograms there was no significant change in the diameter of the inferior vena cava during pressure breathing. In the anteroposterior roentgenograms the borders of the inferior vena cava were not always clearly seen because of the overlying vertebral shadows; therefore, the data are incomplete but in those roentgenograms showing the inferior vena cava clearly there was a signifiant decrease in its diameter during both types of pressure breathing. There was a difference in the effect of continuous and intermittent pressure, the former causing a constant decrease, the latter causing a decrease during the inspiratory phase, that is, when the pressure was high (Table VI). In contrast to these findings, it was shown by direct observation that the abdominal vena cava was dilated during pressure breathing of either type. Again there was a difference in the effect of the two types. During continuous positive pressure respiration the abdominal vena cava remained distended whereas, during intermittent positive pressure respiration, the vessel decreased in size during expiration, when the respiratory pressure was low.

Comment: The diameter of the inferior vena cava was decreased in only the anteroposterior roentgenograms. This may be due to the fact that the inferior vena cava of the dog is in the mediastinal membrane, which is in the

TABLE VI. THE EFFECT OF POSITIVE PRESSURE RESPIRATION ON THE DIAMETERS (IN MILLIMETERS) OF THE INFERIOR VENA CAVA AND THE HEART OF ANIMAL 42

		INFERIOR VENA CAVA		HEART	
		ANTERO-POSTERIOR	LATERAL	ANTERO-POSTERIOR	LATERAL
Normal pressure respiration	Inspiration	12.0	10.0	74.0	74.0
	Expiration	12.0	11.0	74.0	72.0
Continuous positive pressure respiration	Inspiration	9.0		74.0	
	Expiration	9.0	11.0	72.0	69.0
Intermittent positive pressure respiration	Inspiration	9.0	10.0	70.0	67.0
	Expiration	10.0	10.5	74.0	73.0

anteroposterior plane, so that the vessel is more easily compressed from side to side than from front to back. Furthermore, during pressure breathing, the thoracic cage is expanded and the membrane drawn more taut than it is during normal respiration.

Herrick, Mann, Essex, and Baldes[23] have demonstrated previously that, although normal respiration produced no change in the diameter of the inferior vena cava of an anesthetized dog, there was a 5 per cent decrease in the diameter of the inferior vena cava when the animal was given artificial respiration (probably a type of positive pressure respiration).

However, it should be noted that Franklin and Janker[24, 25] have reported that studies of cats, dogs, and rabbits showed that during normal inspiration the inferior vena cava lengthened and decreased in caliber.

III. THE EFFECTS OF POSITIVE PRESSURE RESPIRATION ON THE CIRCULATION AND RESPIRATION WHEN COMBINED WITH ACUTE HEMORRHAGE OR TRAUMA OF LIMBS

Acute Hemorrhage.—Methods: These experiments were carried out in the same way as those described in Section I, except that either before or during the period of pressure breathing, the animal was bled 30 c.c. per kilogram of body weight in a period of five minutes.

Controls: The effect of such a hemorrhage was studied on ten animals while they were breathing at normal respiratory pressure; half of them breathed air and the other half breathed a mixture of 80 per cent helium and 20 per cent oxygen. There was no difference in the results in the two groups. All ten animals survived the experiment and were active and apparently healthy twenty-four hours after the hemorrhage, at which time the blood that had been removed was returned to the animal.

The arterial blood pressure decreased at the time of the hemorrhage in every case, the average dropping from 132 mm. Hg before the hemorrhage to 80 mm. Hg immediately after it (Table VII). In almost every case the blood pressure increased during the further course of the experiment and was higher at the end of the experiment than it was immediately after the hemorrhage.

The venous pressure decreased in nine of the ten animals during the hemorrhage, the average fall being 16 mm. of water. There was no consistent change of the heart rate or the rate of respiration.

TABLE VII. THE EFFECT OF ACUTE HEMORRHAGE (30 C.C. PER KILOGRAM OF BODY WEIGHT IN FIVE MINUTES) ON THE ARTERIAL BLOOD PRESSURE DURING PRESSURE BREATHING*

ANIMAL	ARTERIAL BLOOD PRESSURE IN MM. HG BEFORE AND AFTER HEMORRHAGE		
	CONTROL STUDIES	CONTINUOUS POSITIVE PRESSURE RESPIRATION	INTERMITTENT POSITIVE PRESSURE RESPIRATION
12			110 to 25
13	125 to 75		
14		135 to 30	
17			138 to 30
19	115 to 80		
21	130 to 90		130 to 30
22	155 to 70		
27			100 to 25
28	160 to 140		
32		115 to 25	
33	125 to 105	170 to 85	
37	135 to 20		
38	115 to 70		110 to 50
39	95 to 60		
40	160 to 90		
Average	132 to 80	140 to 47	118 to 32

*The readings were made within one minute before or after the hemorrhage.

Continuous Positive Pressure Respiration: The effect of continuous positive pressure respiration for two to three hours, combined with acute hemorrhage, was studied on eight animals. Three of these were bled while breathing at a continuous positive respiratory pressure of 20 cm. of water (Table VII). One of these survived the hemorrhage and was able to complete the experiment. The arterial blood pressure of the second animal dropped to 25 mm. Hg after only 20 c.c. of blood per kilogram of body weight had been removed. This animal became apneic and died later in the experiment. The arterial blood pressure of the third animal dropped from 135 to 30 mm. Hg during the hemorrhage, and the animal became apneic and died forty-five minutes later. The two animals that died showed a considerable fall of venous pressure at the time of the hemorrhage, 38 and 44 mm. of water, respectively, whereas the venous pressure of the animal that survived showed no fall at all.

The remaining five animals were given a short trial period of continuous positive pressure respiration, following which the respiratory pressure was returned to normal and the animals were bled 30 c.c. per kilogram of body weight in five minutes. Then, following a short recovery period, continuous positive pressure respiration was resumed. Only two of the five animals survived. Two of the others died during the period of pressure breathing, and the third died after the pressure had been discontinued.

When continuous positive pressure respiration was resumed after the hemorrhage, there was a fall of the arterial blood pressure in four of the five animals, the average dropping from 92 to 71 mm. of mercury. With one exception the animals showing the largest falls were the ones that died. Even more striking were the venous pressure measurements; the two animals that survived had a marked elevation of venous pressure (51 and 90 mm. of water) when continuous positive pressure respiration was resumed after the hemorrhage, and this elevation was sustained. In contrast, the animals that died

showed a smaller increase in venous pressure when continuous positive pressure respiration was resumed (19 and 25 mm. of water), and even the small increase was not sustained.

The heart rate and respiratory rate did not show consistent changes.

Intermittent Positive Pressure Respiration: The effect of acute hemorrhage on dogs while they were breathing at an intermittent positive respiratory pressure of 20 cm. of water was studied in five experiments. After thirty minutes of pressure breathing each animal was bled 30 c.c. per kilogram of body weight in five minutes, the positive respiratory pressure being continued during and after the hemorrhage. Three of the animals recovered from the effects of the hemorrhage and were able to complete the three hours of pressure breathing, but the other two showed no tendency to recover until after 10 c.c. of blood per kilogram of body weight had been returned to them.

Immediately after the hemorrhage the arterial blood pressure of the five animals varied from 25 to 50 mm. Hg, the average being 32 mm. of mercury. Before the hemorrhage the pressure had varied from 100 to 138 with an average of 118 mm. of mercury. Three of the animals had a gradual rise of blood pressure following the hemorrhage, and they recovered spontaneously. The arterial blood pressure of the other two remained so low that 10 c.c. of blood per kilogram of body weight was given intravenously to prevent their death.

There was no consistent change in the heart or respiratory rates.

Comment: The control studies demonstrated that normal dogs could withstand a hemorrhage of 30 c.c. per kilogram of body weight in five minutes without difficulty. This has been reported previously by many different workers.[26-28] Such a hemorrhage during pressure breathing of either type was followed by much more serious effects and death in a high percentage of cases. Similar results have been reported by Beecher, Bennett and Bassett.[29]

The average blood pressure following hemorrhage in the control group was 80 mm. of mercury. In contrast to this are the averages of 47 and 32 mm. Hg that obtained in the two groups that were bled during pressure breathing of the two types.

Complete venous pressure studies are not available because of technical difficulties in some cases. However, it was noted that those animals that maintained a high venous pressure after the hemorrhage were able to complete the experiment satisfactorily. Those that had a persistently low venous pressure usually died or had to be given blood intravenously to prevent death.

Obviously there is a significant relationship between the blood volume, the venous pressure, the arterial pressure, and survival during pressure breathing. During positive pressure respiration the flow of blood from the periphery to the right heart is impeded by the tamponade effect of the positive intrathoracic pressure. To some extent this is compensated by a high venous pressure, which is maintained as long as the blood volume and venous tone are normal. When the blood volume is reduced as in hemorrhage the venous pressure is no longer maintained and there is a further decrease of the flow of blood to the right side of the heart. Consequently there is a further decrease of the cardiac output

and the arterial blood pressure, which may result in death. Such a fatality can usually be prevented by increasing the blood volume or discontinuing the positive respiratory pressure.

The importance of the spleen in maintaining an adequate blood volume and enabling the dog to withstand hemorrhage during intermittent positive pressure respiration was demonstrated in two experiments on splenectomized animals. In the first the animal was bled only 20 c.c. per kilogram of body weight, but the arterial blood pressure dropped from 124 to 25 mm. Hg and the animal died eight minutes later. The arterial blood pressure of the second animal dropped from 90 to 35 mm. Hg after a hemorrhage of only 10 c.c. per kilogram of body weight. Normally, the spleen serves as a reservoir of blood on which the animal can call in an emergency, and this is of increased significance during barbiturate anesthesia because of the dilatation of the spleen that takes place when one of that series of drugs is given. Lehman and Amole[30] have shown that after splenectomy dogs anesthetized with sodium amytal are more susceptible to hemorrhage than before splenectomy, but we[27] have shown that splenectomized dogs under pentobarbital sodium anesthesia can be bled 30 c.c. per kilogram of body weight in five minutes with a low mortality rate, when they are breathing at normal respiratory pressure. The untoward reaction of the splenectomized animals to such a small hemorrhage, while breathing at an intermittent positive respiratory pressure of 20 cm. of water, was apparently due to the small decrease of the blood volume, for which there was inadequate compensation. This would seem to emphasize the importance of the relationship between blood volume and survival during pressure breathing.

Limb Trauma.—Method: These experiments were carried out in the same manner as those described in Section I, except that during the period of pressure breathing the hind limbs of the anesthetized animals were clipped free of hair and traumatized with a rawhide mallet weighing 177 Gm. for a total of thirty minutes. Both legs were treated at the same time, first a few blows to one and then a few to the other, care being taken not to break the skin or fracture the bones.

Controls: The four animals in this group were given trauma to both hind limbs while breathing air at normal respiratory pressure. The arterial blood pressure dropped to an average of 50 mm. Hg immediately after the trauma. There was a gradual increase of the arterial pressure for a while, but this was not sustained. The pressure decreased and the animals died after 69, 158, 251, and 207 minutes, respectively.

The venous pressure decreased in each animal immediately after the trauma, the decrease varying from 6 to 50 mm. of water with an average of 22 mm. of water.

The respiratory rate usually increased after the trauma. There was no consistent change in the heart rate.

Intermittent Positive Pressure Respiration: Four animals were given hind-limb trauma during intermittent positive pressure respiration. After the trauma the arterial blood pressure dropped to an average of 42 mm. Hg and showed

little or no tendency to recover while the positive respiratory pressure was continued. It was repeatedly demonstrated that returning the respiratory pressure to normal would be followed by an increase of the arterial blood pressure. These recovery periods apparently prolonged the lives of the animals, but death occurred 108, 180, 170, and 188 minutes after the trauma.

The venous pressures in this group of animals had shown marked increases during the half hour of pressure breathing prior to the period of limb trauma, varying from 19 to 83 mm. of water with an average of 38 mm. of water. After the trauma there was an average decrease of 28 mm. of water.

The trauma was not followed by any consistent change in the heart or respiratory rates.

Comment: Blalock[31, 32] and others[33, 34] have shown that the effects of hind-limb trauma are essentially the same as those of acute hemorrhage. As might have been predicted, we found that the effects of hind-limb trauma during pressure breathing were essentially the same as the effects of acute hemorrhage during pressure breathing. The reduction of the blood volume due to the hemorrhage into the tissues of the legs apparently upset the delicate balance that existed between the blood volume, the venous pressure, and the arterial pressure. If the animals had not been given numerous periods of respite from the positive respiratory pressure, they undoubtedly would have died much sooner.

IV. PULMONARY EMPHYSEMA FOLLOWING PROLONGED POSITIVE PRESSURE RESPIRATION

In each of the foregoing experiments attention was directed to the physiologic aspects and a thorough study was not made of the lungs of the animals that died. However, a gross necropsy was performed on each one and in no instance was pneumothorax, mediastinal emphysema, or gross damage to the lungs observed. Nevertheless, it seemed desirable to study carefully the lungs of a series of animals that had been given three hours of pressure breathing of each type.

Methods.—These experiments were performed as described under Section I, except that the arterial and venous blood pressures were not measured. A series of eleven animals was studied. Three of them were used as normal controls and had no positive pressure respiration. Five were given continuous positive pressure respiration with a pressure of 20 cm. of water; four of these survived the planned period of three hours, but the fifth died after forty-seven minutes of pressure breathing. The remaining three animals were given intermittent positive pressure respiration with a pressure of 15 cm. of water for three hours because the intermittent pressure demand regulator had broken and had been replaced with an instrument that delivered only 15 cm. of water pressure. At the end of each experiment the animal was exsanguinated and necropsy was performed at once. The lungs and trachea were removed intact and, after a careful gross examination, the lungs were sectioned with a sharp knife and fixed in 10 per cent formalin for twenty-four hours. At the end of that time two small blocks of tissue were taken from the apex, the middle lobe, and the base of each lung for histologic sections.

Controls.—Necropsy of these animals revealed no evidence of pneumothorax or mediastinal emphysema. The lungs were crepitant throughout and there was no subpleural or interstitial emphysema. Microscopic examination of the histologic sections revealed a small number of freshly torn alveolar walls but no large emphysematous regions or subpleural emphysematous blebs.

Continuous Positive Pressure Respiration.—Necropsy revealed no evidence of pneumothorax or mediastinal emphysema. When the lungs were removed from the thorax, numerous emphysematous blebs having a diameter of 1 to 3 mm. could be seen beneath the pleura. These were scattered diffusely over both lungs but were most numerous near the lung roots, where they coalesced to form larger emphysematous blebs. The blebs collapsed easily on pressure or when punctured with a needle. The cut section revealed multiple blebs having a diameter of 1 to 2 mm. throughout the lung tissue. Microscopic study of the histologic sections revealed many torn alveolar walls. In many regions there was extensive damage with emphysematous regions measuring 1 to 2 mm. across. In some places the visceral pleura had been separated from the subpleural tissue by a collection of air (Fig. 3).

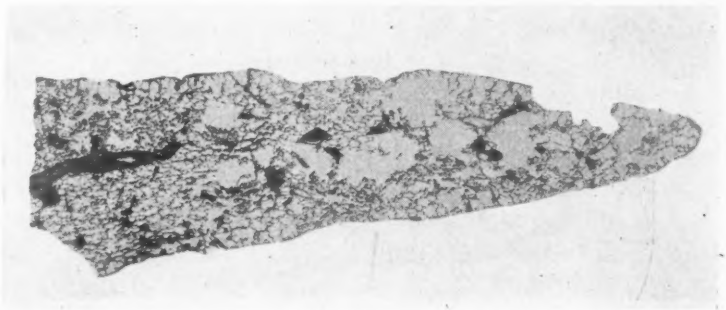

Fig. 3.—Emphysema present after three hours of continuous positive pressure respiration with a pressure of 20 cm. of water. At the upper right margin was a large bulla, the outer margin of which does not show (×8).

Intermittent Positive Pressure Respiration.—There was no evidence of pneumothorax or mediastinal emphysema when these animals were examined. The lungs showed the same type of changes, both gross and microscopic, as those from the animals that had had continuous positive pressure respiration but the damage was less extensive.

Comment.—There have been many previous studies of the effect of increased intrapulmonary pressure on the pulmonary parenchyma. In 1931, Joannides[35] reported that inflation of the lungs of dogs with a pressure of 60 to 100 mm. Hg invariably produced pulmonary emphysema, pneumothorax, pneumoperitoneum, and air embolism. However, he found that 25 to 35 mm. Hg pressure was harmless and he thought it to be of value in the treatment of pneumonia. Coryllos,[36] in 1938, in a study of mechanical resuscitation, found that the visceral pleura of lungs removed from dogs ruptured only when the intrapulmonary pressure was raised to between 52 and 58 mm. of mercury.

However, Adams and his co-workers[12, 37] found that a positive pressure of 24 mm. Hg routinely caused emphysema in dogs and that only 20 mm. Hg was necessary to produce the same change in cats. Rasmussen and Adams[38] reported, in 1942, that a positive pulmonary pressure of 35 mm. Hg for fifteen minutes at biweekly intervals for a year produced in dogs some acute interstitial and mediastinal emphysema with dilatation of the terminal respiratory units and some breaks in the alveolar walls.

In our experiments we found that a continuous positive respiratory pressure of 20 cm. of water for three hours would cause extensive damage to the pulmonary parenchyma. There were many freshly torn alveolar walls with large emphysematous regions. There were innumerable subpleural emphysematous blebs, but apparently none of them ruptured, as pneumothorax was not observed in any case. Neither was mediastinal emphysema observed. Macklin[39] has shown that air in the interstitial tissue of the lung migrates into the mediastinum easily and it is probable that a longer period of pressure breathing would have produced mediastinal emphysema.

The intermittent positive respiratory pressure of 15 cm. of water produced less damage than the continuous pressure of 20 cm. of water. It was also noted that the animal that died of apnea after only forty-seven minutes of continuous positive pressure respiration had less pulmonary damage than any of the four that survived for the three hours of pressure breathing.

SUMMARY

Experimental studies were carried out on dogs anesthetized with pentobarbital sodium to determine the effect of long periods of pressure breathing alone and when combined with acute hemorrhage or trauma of the hind limbs. The following results were obtained:

1. Continuous positive pressure respiration with a pressure of 20 cm. of water.

a. Five of nine animals survived three hours of continuous positive pressure respiration, but, in the case of the other four, fatal apnea developed.

b. The apnea caused by a continuous positive respiratory pressure of 20 cm. of water was not affected by large doses of atropine but was abolished by bilateral vagotomy.

c. Continuous positive pressure respiration had a variable effect on the femoral arterial pressure and on the heart rate. It slowed and deepened the respirations. It elevated the jugular venous pressure, the renal venous pressure, the pulmonary arterial pressure, and the pulmonary venous pressure. It decreased the diameter of the heart and thoracic inferior vena cava but increased the diameter of the abdominal vena cava. It dilated the tracheobronchial tree.

d. Three of eight animals survived two hours of continuous positive pressure respiration after a hemorrhage of 30 c.c. per kilogram of body weight in five minutes, but in the case of the other five animals either apnea or circulatory failures developed.

e. Three hours of continuous positive pressure respiration did not cause either pneumothorax or mediastinal emphysema in a single case, but in all of a group of five animals acute parenchymal and subpleural emphysema developed.

2. Intermittent positive pressure respiration with a pressure of 20 cm. of water.

a. All of a group of five animals withstood three hours of intermittent positive pressure respiration without difficulty.

b. Intermittent positive pressure respiration produced considerable fluctuation of the femoral arterial pressure with a decrease of the mean pressure. It elevated the jugular venous pressure, the pulmonary venous pressure, the renal venous pressure, and the pulmonary arterial pressure. It decreased the diameter of the heart and thoracic inferior vena cava but increased the diameter of the abdominal vena cava and the tracheobronchial tree. It slowed and deepened the respirations but had no consistent effect on the heart rate.

c. Three of five animals survived, without difficulty, two and a half hours of intermittent positive pressure respiration following a hemorrhage of 30 c.c. per kilogram of body weight in five minutes. In the case of the other two, circulatory failure developed and the animals were given 10 c.c. of blood per kilogram of body weight with such improvement that they were then able to complete the experiment.

d. Splenectomized animals were unable to withstand even a small hemorrhage (10 to 20 c.c. per kilogram of body weight) during intermittent positive pressure respiration.

e. Trauma to the hind limbs during intermittent positive pressure respiration proved fatal to all four animals. It was demonstrated that the pressure breathing was a definite factor in hastening their death.

f. Three hours of intermittent positive pressure respiration with a pressure of 15 cm. of water did not cause either pneumothorax or mediastinal emphysema in a single case, but in all of a group of three animals acute parenchymal and subpleural emphysema developed.

CONCLUSIONS

On the basis of experimental studies of continuous positive pressure respiration and intermittent positive pressure respiration carried out on dogs anesthetized with pentobarbital sodium the following conclusions are drawn:

1. Pressure breathing, either continuous or intermittent in type, slows and deepens the respirations.

2. A continuous positive respiratory pressure may cause fatal apnea in the anesthetized animal. This apnea is not affected by the administration of atropine but is not produced in the vagotomized animal.

3. Both types of pressure breathing cause an elevation of the peripheral venous pressure, apparently due to the increased intrathoracic pressure producing a cardiac tamponade.

4. Intermittent positive pressure respiration causes a characteristic fluctuation of the arterial blood pressure with a decrease of the mean pressure but a continuous positive respiratory pressure has no consistent effect.

5. Neither type of pressure breathing has a consistent effect on the heart rate.

6. Both types of pressure breathing dilate the tracheobronchial tree and decrease the diameter of the heart and inferior vena cava but dilate the abdominal vena cava and elevate the renal venous pressure. They increase the pulmonary arterial and venous pressures.

7. Both types of pressure breathing produce acute parenchymal and subpleural emphysema when given over a period of three hours.

8. Either type of pressure breathing increases the risk of an acute hemorrhage. This risk is even greater in splenectomized animals. There seems to be an intimate relation between the blood volume, the venous pressure, and survival during pressure breathing. As long as the venous pressure remains elevated, enough blood seems to return to the heart to maintain a satisfactory although decreased cardiac output. If the venous pressure decreases because of either a loss of venous tone or decreased blood volume, there is apparently a further decrease of the flow of blood into the right side of the heart and the cardiac output is no longer adequate. When this condition develops, either restoring the blood volume or discontinuing the pressure breathing usually results in immediate improvement in the condition of the animal.

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BIGEMINY

An Electrocardiographic Study of Bigeminal Rhythms

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BIGEMINY is a comparatively common electrocardiographic anomaly. In a review of approximately 12,000 tracings, we encountered 95 examples of extrasystolic bigeminy. Coupled rhythm in our material was exceeded in frequency only by the following arrhythmias: sinus tachycardia, sinus bradycardia, sinus arrhythmia, premature contractions in general, and auricular fibrillation. Despite its frequency and clinical importance, bigeminy has attracted but little attention in the literature, particularly in this country. We believe, therefore, that a detailed analysis of the electrocardiographic manifestations of this arrhythmia might prove interesting and of practical benefit.

In approaching this subject, it is necessary to keep in mind the following points: In the first place, bigeminy may be a central phenomenon, a peripheral one, or both. Frustrated premature ventricular contractions after each normal systole give rise to a central bigeminy, but not to a peripheral one. If, on the other hand, the premature beats are effectual, the coupled rhythm may be detected both by auscultation of the heart and by palpation of the radial pulse. Frustrated ventricular extrasystoles after every second normal heartbeat cause a central trigeminy, but a peripheral bigeminy. In the second place, coupling of beats may involve either the auricles or ventricles alone, or both sets of chambers together. An example of auricular, but not ventricular, bigeminy is the occurrence of blocked auricular extrasystoles after each normal heartbeat. If, however, the impulses from these auricular extrasystoles are conducted to the ventricle, both auricular and ventricular contractions are paired. Blocked auricular extrasystoles after every second normal beat result in an auricular trigeminal, but yentricular bigeminal, rhythm. Finally, in the third place, bigeminy may occur as a purely clinical phenomenon. In the case of pulsus alternans the weaker beats are delayed in their transmission to the pulse. This results in a peripheral bigeminy, while the electrocardiogram reveals a regular rhythm.

For our present purpose we shall limit ourselves to a consideration of electrocardiographic bigeminy. We may, then, define electrocardiographic bigeminy as *that phenomenon in which there is a constantly repeated pairing of impulses with respect to time, which involves either the auricles or ventricles alone, or both sets of chambers together.* By definition we are excluding purely clinical forms of bigeminy and also the qualitative pairing of impulses such as electrical alternans, two-to-one bundle branch block, and bidirectional complexes. In this communication we shall attempt to bring the classification of

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electrocardiographic bigeminy up to date, to discuss briefly each type, and to present interesting illustrations of the types which we have observed.

CLASSIFICATION

Benaros[1] offered the most comprehensive classification of bigeminal rhythms which we were able to find in the literature. He discussed the following types: sinusal bigeminy, bigeminy due to sinoauricular or incomplete auriculoventricular block, auricular flutter with varying block, auricular flutter with ventricular extrasystoles, and extrasystolic bigeminy. More recently, Stewart[2] presented a classification of bigeminy which was essentially similar to that of Benaros. Clerc, Levy, and Calo[3] discussed sinusal bigeminy in great detail. Although the exact differentiation of the theoretical types of sinusal bigeminy is perhaps impossible with present limitations of our knowledge, we have nevertheless, for the sake of completeness incorporated their classification into our own, which follows:

ELECTROCARDIOGRAPHIC BIGEMINAL RHYTHMS

I. Extrasystolic bigeminy
  A. Sinus nodal
  B. Auricular
    1. Conducted auricular extrasystoles (auricular and ventricular bigeminy)
    2. Blocked auricular extrasystoles
      a. After each normal beat (auricular bigeminy)
      b. After each second normal beat (auricular trigeminy, ventricular bigeminy)
  C. A-V nodal
  D. His bundle
  E. Ventricular
    1. Right ventricular
    2. Left ventricular
    3. Septal

II. Sinusal bigeminy
  A. Sinus pauses
    1. Delay in impulse formation
    2. Failure of impulse formation
  B. Alternation of sinoauricular conduction
  C. Three-to-two sinoauricular block
    1. With Wenckebach's phenomenon
    2. Without Wenckebach's phenomenon

III. Bigeminy due to auriculoventricular block
  A. Alternation of P-R interval
  B. Three-to-two A-V block (with nomotopic rhythms, paroxysmal auricular tachycardia, or auricular flutter)
  C. High-grade A-V block with escape beats
  D. Alternating degrees of auriculoventricular block (two-to-one with three-to-one or four-to-one, etc.)
    1. With normal sinus rhythm
    2. With auricular flutter
  E. Two-to-one A-V block with alternation of auricular cycle length (auricular bigeminy)

IV. Auriculoventricular nodal bigeminy
  A. Reciprocal rhythm

B. Pseudoreciprocal rhythm
C. Nodal rhythm and premature contractions
D. Premature contractions paired with nodal escape beats

V. Bigeminy due to alternation of short P-R, wide QRS complexes, with normal complexes.

VI. Bigeminy due to fortuitous pairing of ventricular responses in auricular fibrillation

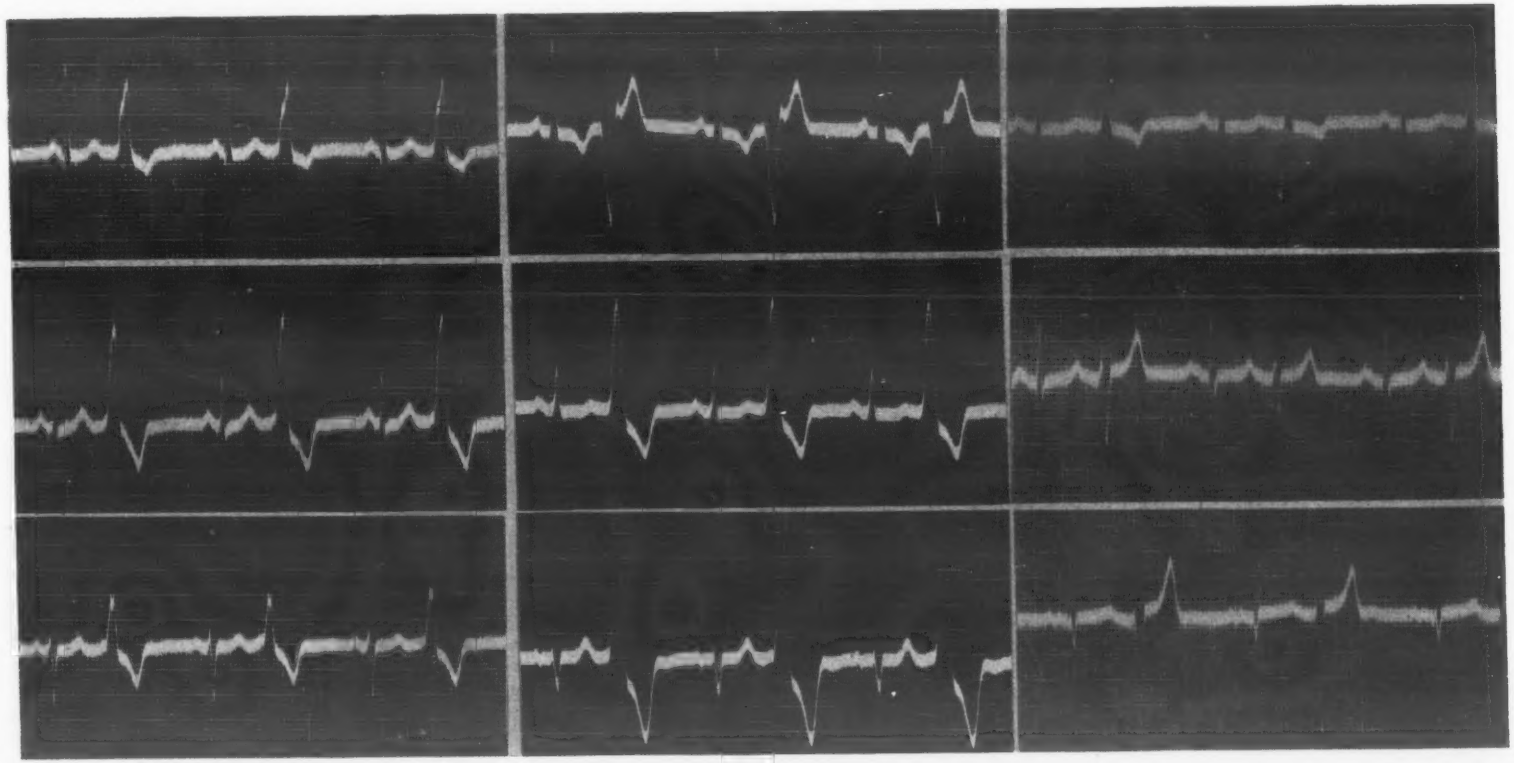
VII. Bigeminy due to alternation of cycle length in paroxysmal auricular tachycardia

Extrasystolic Bigeminy.—By far the most common type of bigeminy is the occurrence of premature contractions after each normal heartbeat, the classical "pulsus bigeminus." This allorhythmia assumes particular importance for the following reasons: (1) It is generally conceded that the pathologic significance of premature beats varies directly with the frequency of their occurrence; this frequency reaches a theoretical maximum in a bigeminal rhythm. (2) This arrhythmia is seen commonly during the course of digitalis therapy; it is a sign of digitalis intoxication and is usually an urgent indication for the temporary withdrawal of the drug. (3) Pulsus bigeminus may be confused clinically with other types of bigeminy which may be of more ominous prognostic import, e.g., pulsus alternans. (4) Finally, the frequent occurrence of extrasystoles in a bigeminal rhythm affords an exceptional opportunity for the study of the underlying mechanism of extrasystoles in general.

The premature contractions may originate in the sinus node, the auricles, the auriculoventricular node, the His bundle, or the ventricles. In our series, the ectopic focus was situated in the ventricles in 78 cases, in the auricles in nine, and in the auriculoventricular node in six. We did not encounter any examples of His bundle or sinoauricular premature contractions. Although theoretically a premature beat might arise from some region in the sinus node other than the normal pacemaker, we know of no reliable criteria by which it could be differentiated from an auricular beat of juxtasinusal origin, or from variations in sinoauricular conduction.

Bigeminy Due to Premature Ventricular Contractions.—Premature ventricular contractions may originate in the right or left ventricle or in the region of the interventricular septum. The criteria for determining the site of origin are based upon the observations of Barker, Macleod, and Alexander.[4] Right ventricular extrasystoles are characterized by an upright, and left ventricular extrasystoles are characterized by an inverted, major deflection of the QRS complex in Lead I. If the major QRS deflections are in the same direction in all leads, the extrasystoles are said to be of the concordant type. If the major QRS deflections in Leads I and III point in opposite directions, the extrasystoles are termed discordant. In the case of septal extrasystoles, the QRS complexes are of either normal or slightly increased width, and are only slightly aberrant in contour (Fig. 1).

In our series of 78 cases we found 35 instances of left ventricular extrasystoles, 39 of right ventricular extrasystoles, and one of the septal type. In the remaining three cases the localization was indeterminate. No correlation was detected between the site of origin of the extrasystole and preponderance of either ventricle. Of the right ventricular extrasystoles, 20 were of the discordant



A. *B.* *C.*

Fig. 1.—*A*, Concordant right ventricular extrasystoles; fixed coupling. *B*, Discordant left ventricular extrasystoles; coupling not fixed. *C*, Septal extrasystoles; QRS of ectopic beats 0.10 second in duration.

type and 10 were of the concordant type. Of the left ventricular extrasystoles, 21 were discordant and three were concordant. In the remaining 24 cases, it was not possible to determine concordance for several reasons, namely, absence of premature beats in one of the leads, multifocal sites of origin, or polyphasic QRS complexes.

Ventricular extrasystolic bigeminy occurred in association with the following auricular mechanisms: normal sinus rhythm, sinus tachycardia, sinus arrhythmia, normal sinus rhythm with auricular extrasystoles, and auricular fibrillation. It is possible that some of the cases may have been instances of sinus bradycardia with interpolated ventricular extrasystoles. This possibility can be proved only if the extrasystoles disappear without a resultant change in the interval between

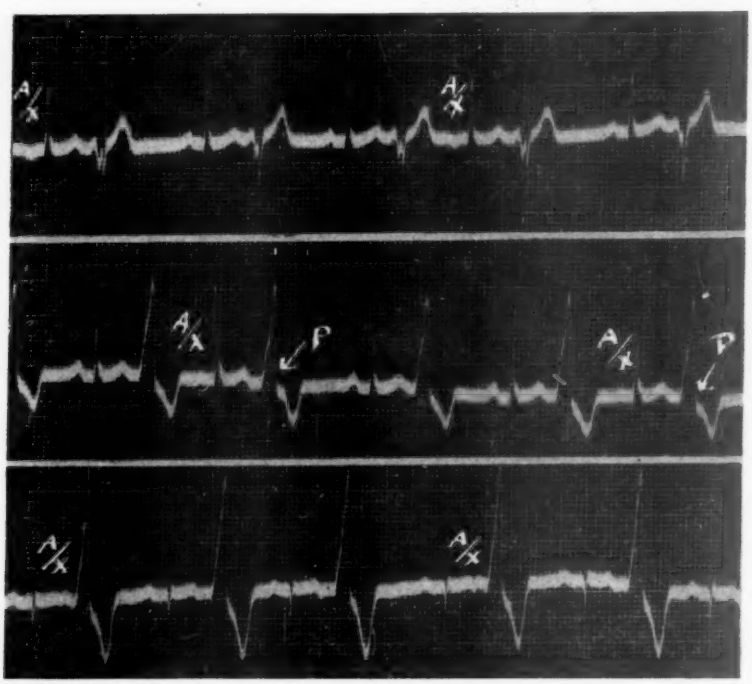


Fig. 2.—Discordant left ventricular extrasystoles paired with each normal beat. Fixed coupling. Auricular rhythm disturbed by auricular extrasystoles after each fifth auricular beat.

sinus beats. Ventricular extrasystoles complicating auricular flutter have also been reported. Auricular fibrillation was present in the high proportion of 32 (42 per cent) of the 78 cases. The explanation for this fact is that a large percentage of these patients were receiving digitalis, and, furthermore, both auricular fibrillation and pulsus bigeminus are seen most often in hearts which are diseased. Complete heart block was present in three cases. In the latter, then, the premature contractions were coupled with an idioventricular rhythm. Ventricular extrasystoles also may be coupled with a dominant auriculoventricular nodal rhythm (q. v.).

Fig. 2 illustrates ventricular extrasystoles associated with a normal sinus rhythm and auricular extrasystoles. Discordant left ventricular extrasystoles follow each normal heartbeat. The sinus rhythm is disturbed by auricular extrasystoles of left auricular origin, as indicated by the inverted P wave in Lead I and upright P waves in Leads II and III. At first glance the auricular extrasystoles appear to occur in trigeminy. However, on close scrutiny of Lead II, in the T wave of the ventricular extrasystole following the auricular extrasystole, a P wave may be discerned. The true rate of the dominant rhythm, therefore, is actually twice as fast as it seems, and the auricular extrasystole occurs after every fifth normal auricular beat. Despite the irregular auricular rhythm, the coupling of the ventricular extrasystoles remains fixed.

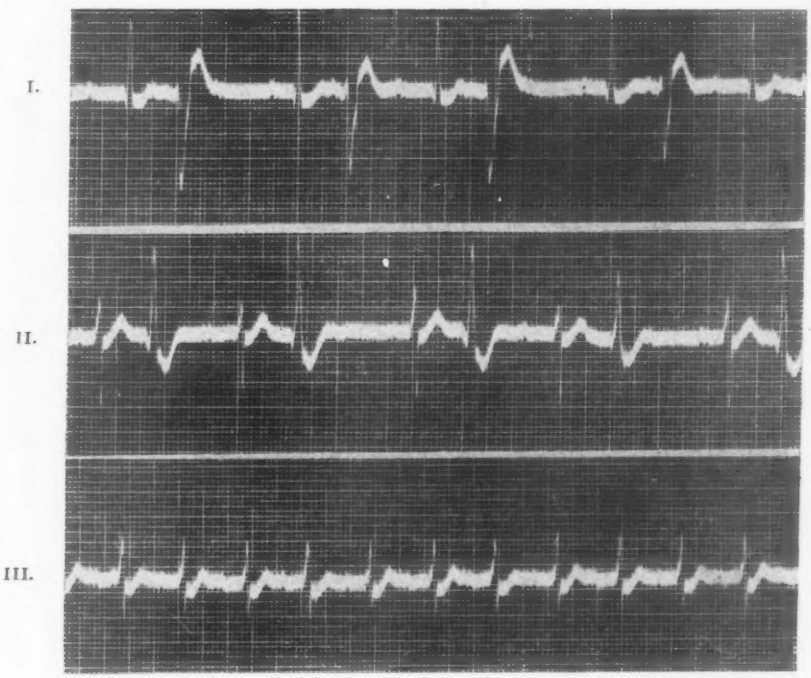


Fig. 3.—Sinus tachycardia, ventricular extrasystolic bigeminy. Extrasystoles cause A-V conduction disturbances in following beats, and ventricular rhythm is consequently irregular.

In Fig. 3 the dominant rhythm is a sinus tachycardia with a rate of about 115 per minute. In Leads I and II, ventricular extrasystoles follow each normal beat. The ventricular extrasystoles cause interference with the normal A-V conduction, so that some auricular beats are delayed in their transmission to the ventricles, and some are completely blocked. The coupling is fixed, despite the irregular dominant ventricular rhythm, with the exception of the fourth pair in Lead II, in which the ectopic beat is probably of a different origin from the others in the tracing.

Fig. 4 is an illustration of ventricular extrasystolic bigeminy in which the dominant rhythm is auricular fibrillation. The extrasystoles originate in the

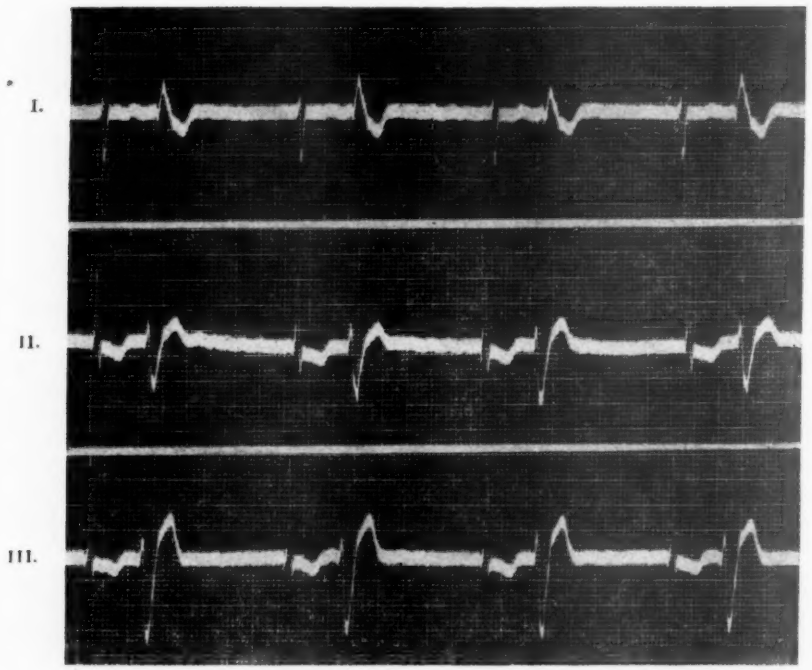


Fig. 4.—Auricular fibrillation, discordant right ventricular extrasystoles; coupling fixed. Note digitalis effects.

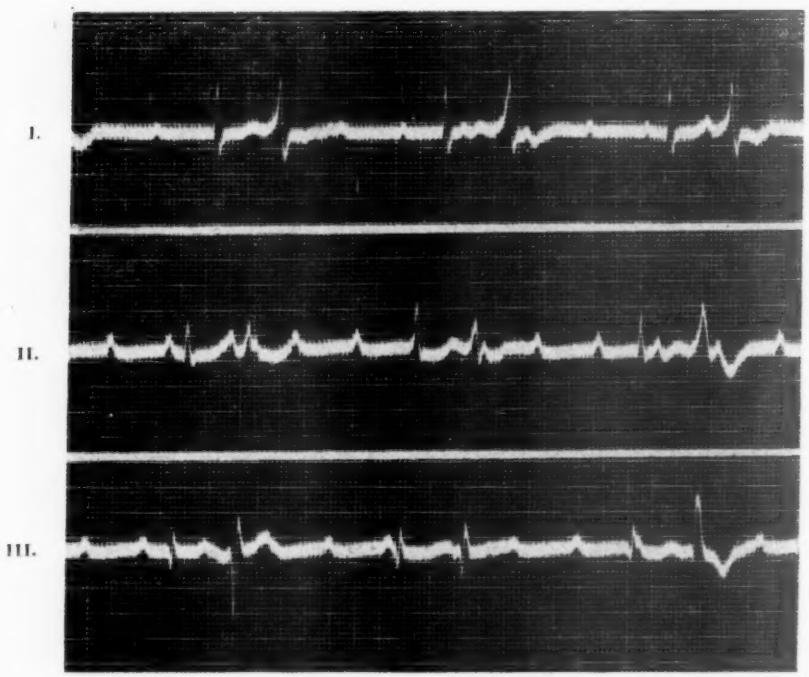


Fig. 5.—Complete auriculoventricular block. Multifocal ventricular extrasystoles paired with dominant idioventricular rhythm.

right ventricle and are discordant in type; the coupling is not fixed. The dominant ventricular rhythm is fairly slow and regular.

Fig. 5 presents an example of complete auriculoventricular block, with ventricular extrasystoles coupled to the idioventricular rhythm. The extrasystoles are multifocal in origin, and the coupling is not fixed.

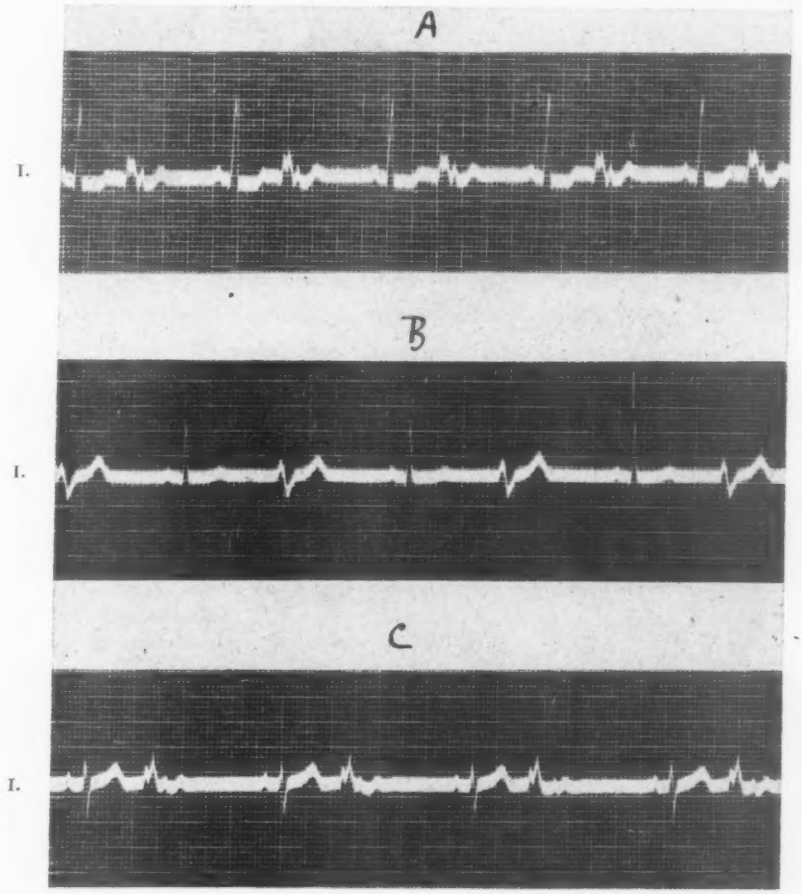


Fig. 6.—*A*, Fixed coupling; *B*, parasystole; *C*, sporadic extrasystoles.

Ventricular extrasystoles may arise from one focus (Fig. 1) or from two or more foci (Fig. 5). When successive premature beats are of markedly varying contours, it is safe to assume that they are of multifocal origin. On the other hand, slight differences in the configuration of the ectopic QRS complexes may be due to change in direction of spread of the impulse from a single focus.[5] Also, since the electrical axis of the impulse stemming from an ectopic focus may be perpendicular to any one of the limb leads, respiratory variations in the initial ventricular deflections may be present in the corresponding lead. Bearing

these facts in mind, we judged 37 of our cases to be of unifocal, and 41 to be of multifocal, origin.

Fixed coupling (Fig. 6,*A*) is believed to be evidence of the re-entry phenomenon. Here, again, there is the difficulty of deciding just what constitutes fixed coupling. It is possible that the re-entrant wave may arrive on time, but that, due to slight local impairment in conduction, discrepancies in the timing of the coupling may follow. Moreover, not infrequently the coupling is fixed in each individual lead but appears to vary from lead to lead. This illusion may be due to an isoelectric beginning of either the normal or ectopic QRS complexes (Fig. 1,*A*).[6] With due consideration to these factors we thought that 40 of our cases exhibited true fixed coupling. If fixed coupling be in fact evidence of re-entry, then theoretically no isoelectric line should be apparent between the two beats. In the majority of our cases this was true, but in some the coupling was fixed, although the premature beat occurred late in diastole, and even after the inscription of the oncoming P wave. Another point of interest in this connection is that, in some cases, the coupling remains fixed although the ectopic beats are of multifocal origin. Digitalis favors re-entry primarily because it causes local changes in refractivity, and not, as is commonly stated, because it causes increased excitability of the myocardium.

The theory of parasystole (Fig. 6,*B*) is based upon the premise that a ventricular ectopic focus is in continual activity and generates impulses at a constant rate, independent of the dominant rhythm. We found only four cases in our series which exhibited this phenomenon. If it be assumed, however, that the rhythm of the ectopic focus may vary, or that multiple parasystolic foci may be simultaneously active, most cases of premature contractions could be explained by this theory.[7]

In 34 of our cases the premature beats appeared at irregular intervals following the normal ventricular complexes, and did not exhibit an independent, regular rhythm; i.e., they conformed neither to the criteria of re-entry nor to the criteria of parasystole (Fig. 6*C*). In this event, the extrasystoles are believed to be due to sporadic activity of an ectopic pacemaker.

We were interested in observing that patients with auricular fibrillation and ventricular bigeminy showed most often a remarkably slow and regular rate. This may have been due to the effect of digitalis, that is, the ventricular rate may have been slow even in the absence of premature beats, and, therefore, their appearance would be favored. An alternative explanation is that the retrograde excitation wave which originated in the ectopic focus may have fatigued the junctional tissues and caused a pseudocompensatory pause.[8]

Auricular Extrasystolic Bigeminy.—Auricular extrasystolic bigeminy (Fig. 7) was encountered nine times in our material. In eight cases there was present a single ectopic focus, and in the last case there were multiple foci. The contour of the P wave depends upon its site of origin; the further removed from the sinus node the ectopic focus is, the more aberrant will be the auricular complex. Left auricular extrasystoles are characterized by an inverted P wave in Lead I and upright P waves in Leads II and III. This type is rare and did not occur

in bigeminy in the present series. Premature beats which originate in the caudal region of the right auricle are theoretically characterized by low voltage P waves in Leads II and III. The P-R interval of conducted premature auricular contractions may be normal, diminished, or prolonged. If an auricular extrasystole after each normal beat is blocked, auricular bigeminy alone will result. On the contrary, blocked auricular extrasystoles after every second normal beat will cause auricular trigeminy, but ventricular bigeminy. The QRS complexes which follow auricular extrasystoles may be normal in contour, or either slightly or markedly aberrant. The coupling of the premature auricular beats in five of our group of cases was fixed. In one there was apparently a parasystolic arrhythmia; in the remaining three cases the premature beats occurred sporadically.

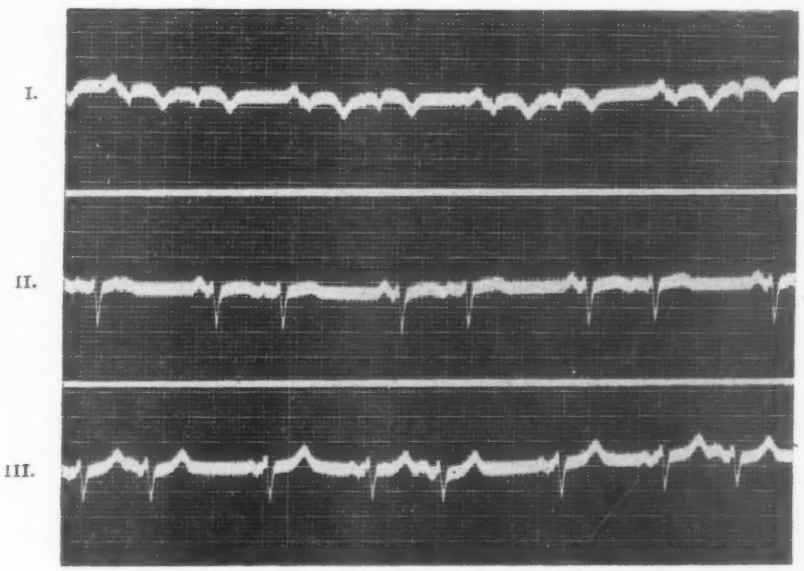


Fig. 7.—Auricular extrasystolic bigeminy.

Fig. 8,*A*, is an interesting example of blocked auricular extrasystoles after each normal beat leading to auricular, but not ventricular, bigeminy. Fig. 8,*B*, taken two weeks later, shows normal sinus rhythm. In Fig. 8,*A*, due to the prolonged postextrasystolic pause, the ventricular rate is slowed to approximately 43 per minute, and the Q-T interval is consequently prolonged to 0.52 second. The Q-T interval during normal rhythm, at a rate of 86 per minute, is 0.36 second.

A-V Nodal Extrasystolic Bigeminy.—Our cases included six instances of premature A-V nodal contractions in bigeminy. We accepted as an impulse of A-V nodal origin one in which the P wave was inverted in Leads II and III, regardless of the P-R interval, and with the QRS complexes normal, slightly aberrant, or markedly aberrant (Fig. 9). In five cases the nodal premature beats were coupled with a normal sinus rhythm, while in the sixth case they were paired

with a dominant nodal rhythm. The latter will be described under the heading of A-V nodal bigeminy. Some overlapping in our classification has been unavoidable.

Sinusal Bigeminy.—Sinoauricular block is the rarest form of heart block. The chance occurrence of three-to-two sinoauricular block giving rise to a bigeminal rhythm is, therefore, extremely rare. It may occur either with or without the Wenckebach phenomenon. Theoretically sinoauricular block must be differentiated from sinus pauses and alternation of sinoauricular conduction.

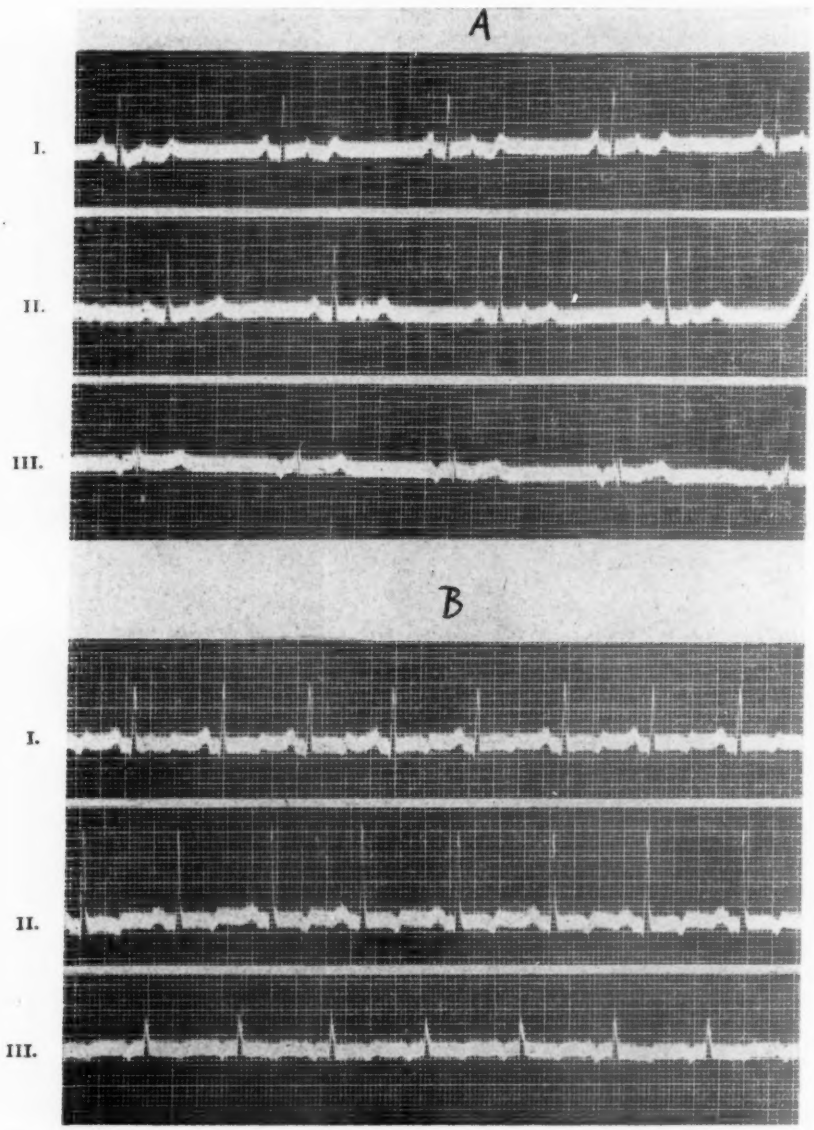


Fig. 8.—*A*, Blocked auricular extrasystoles after each normal beat. *B*, Same patient, electrocardiogram taken two weeks later. Normal sinus rhythm. Note change in Q-T interval.

Sinus pauses may be due to delay in impulse formation, or failure of impulse formation. Three-to-two block may be diagnosed with some degree of assurance only when the longer intervals are exactly twice the duration of the normal interventricular intervals. It is beyond the scope of this paper to discuss in detail the academic differentiation of the various types of irregularities mentioned above. An excellent summary of this subject may be found in the report of Clerc, Levy, and Calo.[3] We encountered one case of sinusal bigeminy in our series.

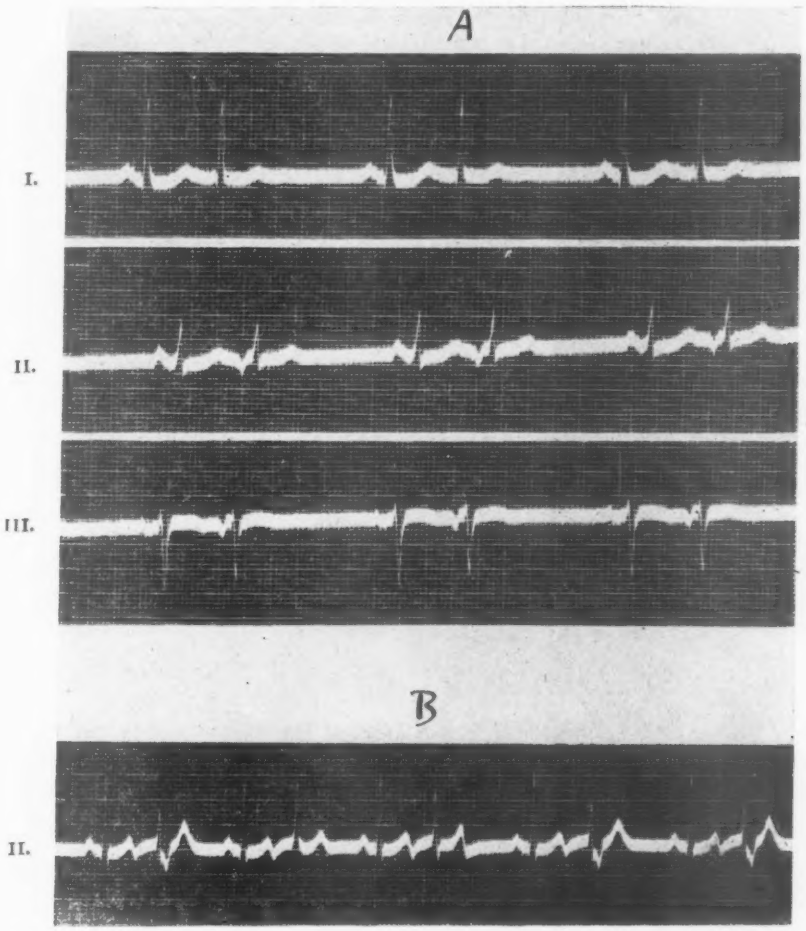


Fig. 9.—*A*, A-V nodal extrasystolic bigeminy; P-R interval shorter than 0.12 second. *B*, A-V nodal extrasystolic bigeminy; aberrant QRS complexes; P-R interval exceeds 0.12 second.

Fig. 10 is an example of sinusal bigeminy due to three-to-two sinus pauses. The contour of the P waves is constant in each lead, and the second beat of each pair is obviously not premature. The pause between pairs of beats is probably due to delay in impulse formation in the normal pacemaker. The pause appears too long to be due to mere alternation in S-A conduction and too

short to be due to a blocked sinus impulse. The fifth ventricular complex in Lead III is a nodal escape beat.

Three-to-two sinoauricular block must be differentiated from auricular extrasystolic bigeminy in which the ectopic focus is of a juxtasinusal origin and from blocked auricular extrasystoles in trigeminy in which the premature auricular complexes are buried in the preceding T wave.

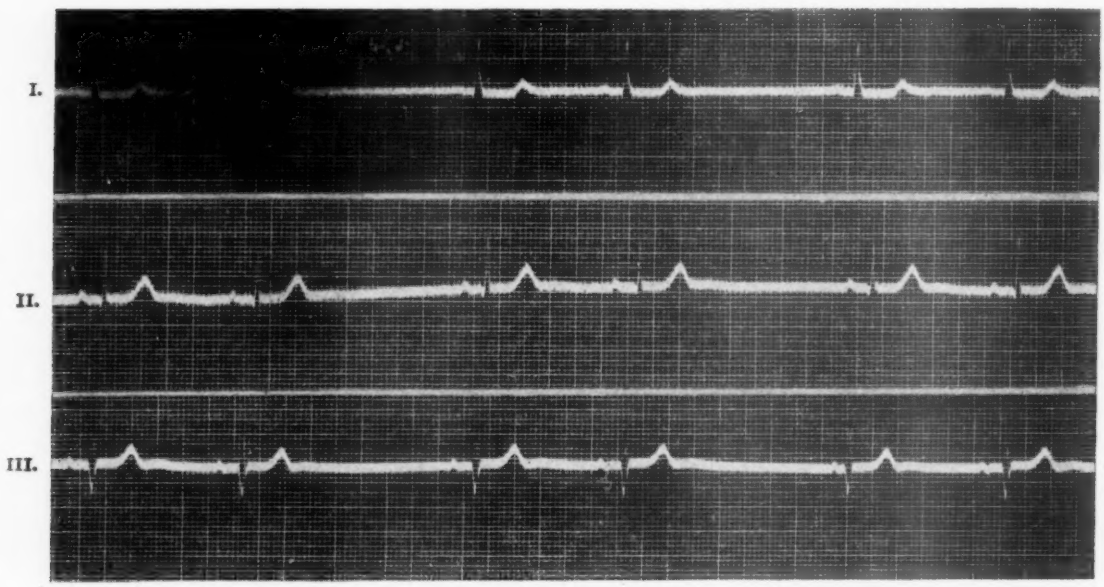


Fig. 10.—Bigeminy due to three-to-two sinus pauses. Fifth QRS complex in Lead III an escape beat.

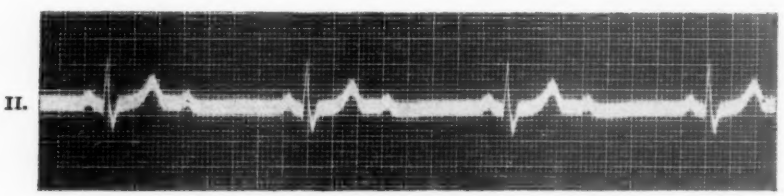


Fig. 11.—Two-to-one A-V block; interauricular intervals during which ventricular systole occurs shorter than those in which ventricular response is blocked. An example of auricular, but not ventricular, bigeminy.

Bigeminy Due to Incomplete Auriculoventricular Block.—Incomplete A-V block may give rise to several different mechanisms which result in bigeminy. Rarely, there may be alternation of the P-R interval.[7] This gives rise to a ventricular but not an auricular, bigeminy. On the other hand, in two-to-one A-V block, the interventricular interval, during which ventricular systole occurs, is often shorter than the interauricular interval in which the ventricular response is blocked. This (Fig. 11) results in an auricular, but not ventricular, bigeminy.[9] Parsonnet and Miller[10] observed this phenomenon in three of eight cases of two-to-one A-V block. Three-to-two auriculoventricular block is a fairly com-

mon phenomenon (Fig. 12). There were nine cases in our series. In three the P-R interval of conducted beats was normal, whereas in the other six cases the Wenckebach phenomenon was present. One case occurred during paroxysmal auricular tachycardia. Three-to-two A-V block may also be seen in auricular flutter. Of particular interest are those rare cases in which the degree of block varies alternately from one-to-one, to two-to-one, three-to-one, et cetera.

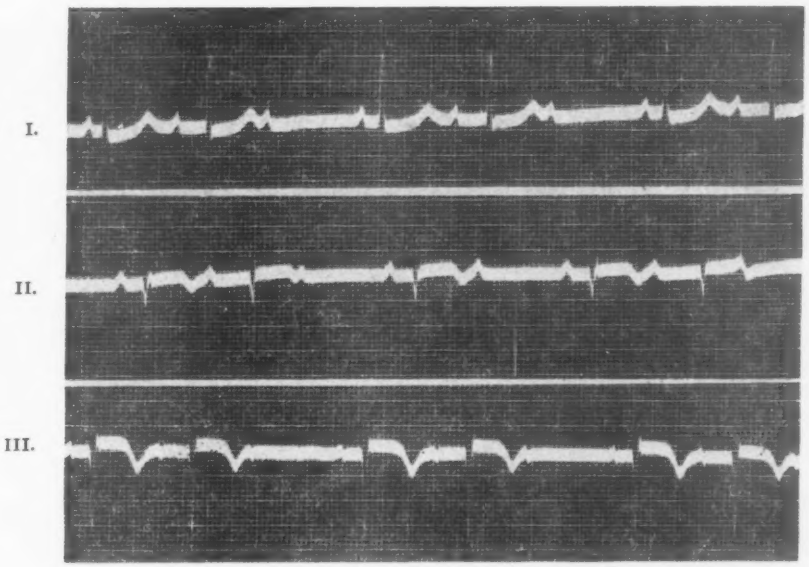


Fig. 12.—Three-to-two A-V block with Wenckebach's phenomenon.

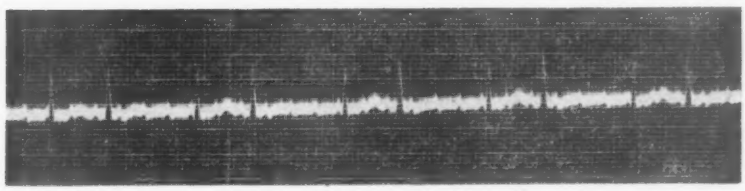


Fig. 13.—Auricular flutter, with degree of A-V block varying from two-to-one to four-to-one.

Lutembacher[11] presented a rare case in which there was variation from one-to-one to two-to-one and three-to-one block during normal sinus rhythm. We encountered one case in which this phenomenon occurred in association with auricular flutter with the A-V block alternating between two-to-one and four-to-one (Fig. 13). In higher degrees of block, nodal escape beats may occur coupled with conducted beats. We had one such case in our series (Fig. 14). A similar one has been reported by von Hoesslin.[9]

Auriculoventricular Nodal Bigeminy.—Regularly recurring reciprocal beats give rise to an unusual form of bigeminy. Reciprocal rhythm is of special interest because it provides indisputable evidence for the phenomenon of re-entry. It is not to be confused with pseudoreciprocal rhythm in which nodal

escape beats are paired with, and precede normal sinus nodal beats. For examples of reciprocal and pseudoreciprocal rhythms, Katz's[7] text may be consulted.

A-V nodal rhythm may be paired with nodal premature contractions (Fig. 15) or ventricular premature contractions (Fig. 16). We encountered one example of each of these varieties of bigeminy. Still another possible variety of nodal bigeminy is that in which nodal premature contractions are coupled with nodal escape beats, with consequent dissociation by interference from the normal sinus rhythm. An example of this phenomenon, which we observed, is illustrated in Fig. 17. We have not been able to find a similar case in the literature, although *The American Illustrated Medical Dictionary,* by Dorland,[12] defines it. The following three illustrations present interesting types of nodal bigeminy.

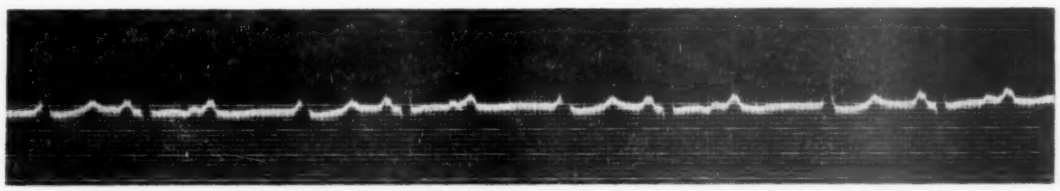


Fig. 14.—Three-to-one A-V block, with nodal escape beats.

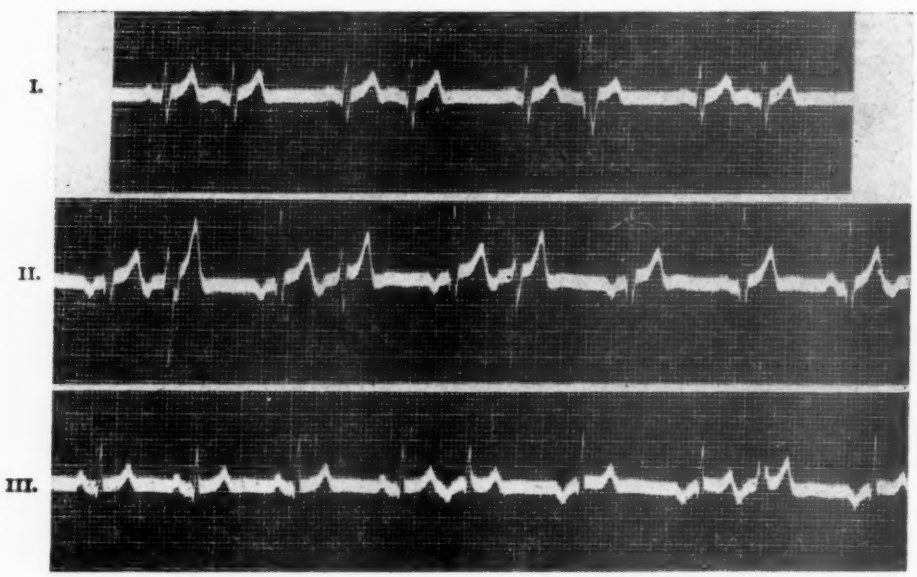


Fig. 15.—Nodal extrasystoles paired with dominant A-V nodal rhythm.

Fig. 15 shows nodal premature contractions paired with a nodal rhythm. This is a complex arrhythmia, which can best be resolved by study of Lead II. In this lead four different types of P waves can be discerned. The ninth P wave is of normal sinus origin, the eighth P wave is probably a transitional complex. The first, third, fifth, and seventh P waves are A-V nodal in origin, and the second,

fourth, and sixth P waves are premature contractions, arising from a different portion of the A-V node. The QRS complexes which correspond to the nodal extrasystoles are slightly to markedly aberrant.

The three tracings in Fig. 16 were taken on the same patient on separate occasions. Fig 16, *A*, shows auricular fibrillation with premature ventricular contractions. In Fig. 16 *B*, auricular fibrillation is present, with a perfectly regular ventricular rhythm, at a rate of about 102 per minute. The ventricles on this occasion must be dominated by a center in the A-V node. In the next tracing (Fig. 16, *C*) the dominant ventricular rhythm is still regular, and therefore nodal in origin, and ventricular extrasystoles follow each normal beat. The auricles are fibrillating.

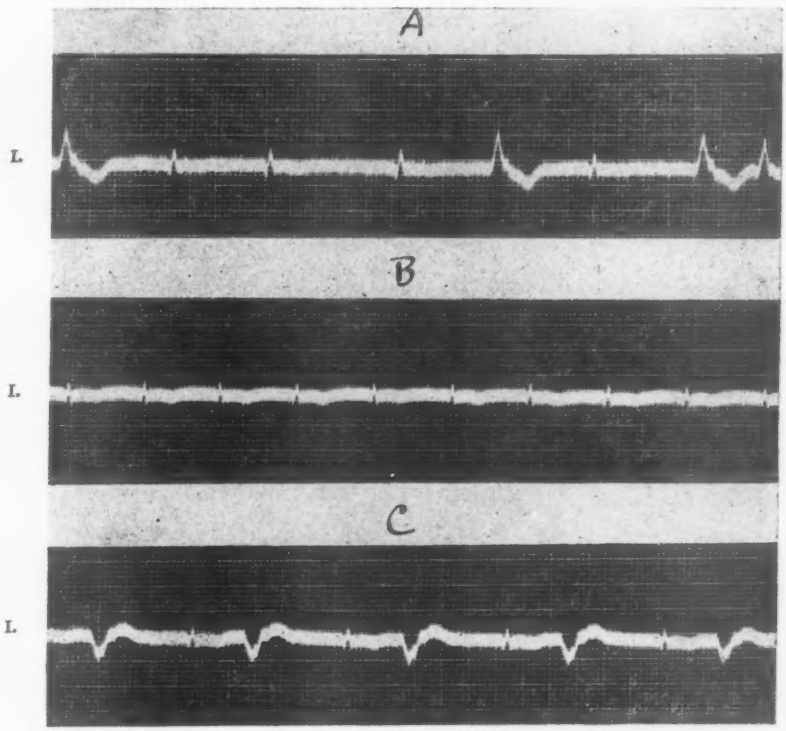


Fig. 16.—Three tracings from the same patient taken on different occasions. *A*, Auricular fibrillation, ventricular extrasystoles. *B*, Auricular fibrillation, A-V nodal rhythm. *C*, Auricular fibrillation, A-V nodal rhythm, ventricular extrasystolic bigeminy.

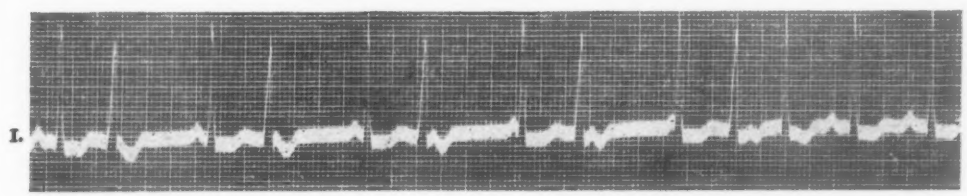


Fig. 17.—Bigeminy due to nodal premature contractions and nodal escape beats.

Fig. 17 exhibits a complex arrhythmia. The auricular rhythm is perfectly regular with a rate of 94 per minute. The first P wave is followed normally by a ventricular response. The second QRS complex is a nodal extrasystole, and the third QRS complex is a nodal escape beat. Nodal escape beats then pair with nodal extrasystoles to cause a bigeminal rhythm. The third, fifth, seventh, and ninth ventricular complexes are nodal escape beats. The second, fourth, sixth, eighth, and tenth are nodal extrasystoles. Due to interference dissociation, the auricular and ventricular rhythms are independent of each other. The auricular impulse which follows the tenth ventricular systole finds the junctional tissues in a relatively refractory state and is transmitted to the ventricle after a prolonged P-R interval of 0.28 second. This terminates the abnormal rhythm, and the eleventh, twelfth, and thirteenth ventricular systoles are in response to the normal pacemaker, with normal A-V conduction. The intervals between nodal premature contractions are constant, as are those between nodal escape beats. The interval between the first normal ventricular systole and the first nodal extrasystole is shorter than the succeeding intervals between nodal escape beats and premature contractions. Therefore, there are either two parasystolic foci with identical inherent rhythms in operation, or the premature nodal beats are due to a parasystolic rhythm, with the escape beats coupled to them.

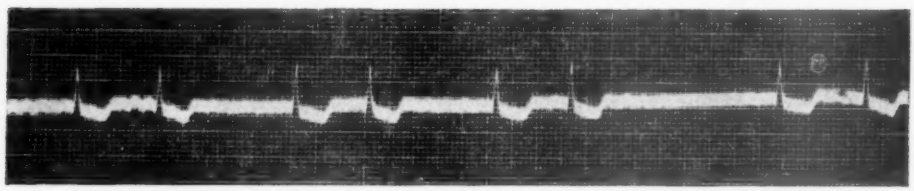


Fig. 18.—Auricular fibrillation with fortuitous pairing of ventricular responses.

Bigeminy Due to Short P-R Interval and Wide QRS Complexes Alternating With Normal Beats.—A most interesting case in which conduction through the normal junctional tissues alternated with conduction through the accessory bundle of Kent was reported by Clagett.[13] The alternation of the P-R interval, in effect, leads to ventricular bigeminy. An observation in this case which particularly intrigued us was that the auricular complexes which preceded the wide QRS complexes were also premature.

Auricular Fibrillation With Fortuitous Pairing of Ventricular Responses.—We have noticed that occasionally in auricular fibrillation, particularly when the ventricular rate is slow, the ventricular responses may be fortuitously grouped in pairs (Fig. 18). Such cases might easily be mistaken for other forms of bigeminy.

Bigeminy Due to Paroxysmal Auricular Tachycardia With Alternation of Cycle Length.—Barker, Johnston, and Wilson[14] have presented cases of auricular paroxysmal tachycardia with alternation of cycle length. Their explanation of this phenomenon is that paroxysmal auricular tachycardia is a form of circus rhythm, with part of the pathway involving one of the specialized nodes. Changes

in the pathway through the node in alternate beats might give rise to the alternation of cycle length of the ventricular responses.

Phenomena Resembling Bigeminy.—Pulsus alternans gives rise to clinical bigeminy by virtue of the fact that the weaker beats are delayed in their transmission to the pulse, due to prolongation of the isometric contraction phase of the left ventricle, so that the pulse beats are paired as to time as well as to volume. Electrocardiographically, however, true bigeminy does not occur. Electrical alternans, also, is not to be considered a true form of bigeminy, because the QRS complexes are paired qualitatively but not in respect to time (Fig. 19).

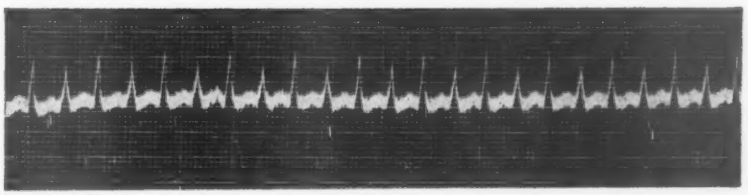


Fig. 19.—Paroxysmal supraventricular tachycardia with electrical alternans. (Qualitative pairing of beats.)

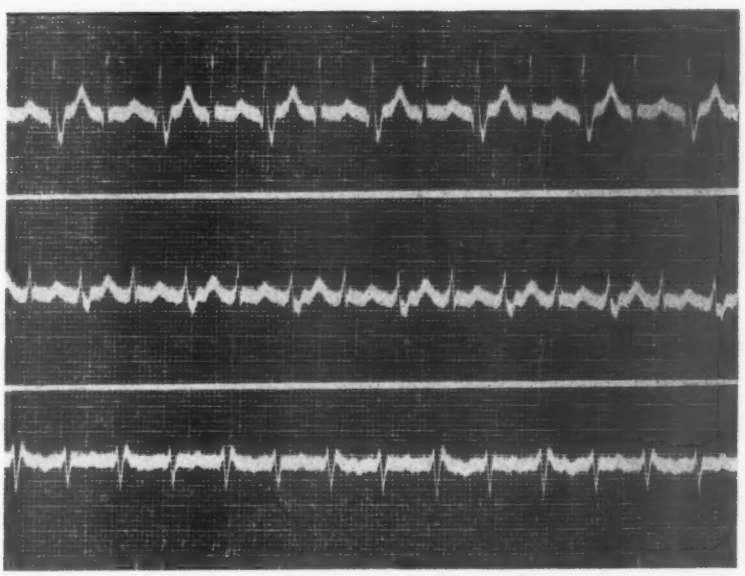


Fig. 20.—Auricular flutter, two-to-one A-V block, two-to-one right bundle branch block. (Qualitative pairing of beats.)

Other forms of qualitative pairing of electrocardiographic complexes are encountered in two-to-one bundle branch block and bidirectional complexes. An example of two-to-one bundle branch block, which at first glance might be mistaken for a true bigeminy, is shown in (Fig. 20). In this case the dominant rhythm is auricular flutter. There is present two-to-one A-V block and also two-to-one right bundle branch block.

SUMMARY

1. Electrocardiographic bigeminy is defined as that phenomenon in which there is a constantly repeated pairing of impulses with respect to time, which involves either the auricles or ventricles alone, or both sets of chambers together.

2. A comprehensive classification of electrocardiographic bigeminy is presented.

3. The various types of electrocardiographic bigeminy are described, and interesting examples which we have observed are shown.

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Clinical Reports

STAPHYLOCOCCUS AUREUS SEPTICEMIA AND PERICARDITIS TREATED WITH PENICILLIN

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PHILADELPHIA, PA.

IN SPITE of the introduction and development of sulfonamides, the treatment of staphylococcic infections and staphylococcic septicemia remained unsatisfactory. Torrey, Julianelle, and McNamee[1] observed sixty-two patients with staphylococcic septicemia and, although these patients were treated with various sulfonamides, the authors were unable to conclude that the course of the infection was altered. They believed that those patients who survived did so presumably as the result of other treatment. Furthermore, since metastatic abscesses occur very frequently in staphylococcic septicemia, the morbidity and mortality in individual instances depends to a large extent upon the site of abscess formation and the accessibility of these abscesses to surgical incision. It has often been necessary to subject these seriously ill patients to major surgical procedures in an effort to relieve localized collections of pus.

The necessity for surgical intervention becomes particularly urgent in instances of staphylococcic pericarditis. Streider and Sandusky,[2] reviewing the subject of pericardiostomy for suppurative pericarditis, stated that the mortality for unoperated patients must approach 100 per cent. Those patients who were operated upon had a 50 per cent mortality, but this figure becomes much higher when the pericarditis is part of a generalized pyemia. We have been able to find only a few reports of recovery through the use of chemotherapy and pericardicentesis.[3-5]

The already proved efficacy of penicillin in the treatment of staphylococcic infections has opened a new method of management in these cases of suppurative pericarditis. It is the purpose of this paper to report the case of a patient with staphylococcus septicemia and staphylococcus pericarditis successfully treated with penicillin administered parenterally and intrapericardially.

REPORT OF CASE

History.—J. B., a 27-year-old Negro laborer, was admitted to the hospital Feb. 7, 1944, complaining of severe pain about the heart. Ten days prior to admission, catheterization had been necessary for urinary retention. This was followed in a few days by chills, fever, sweats, generalized aches and pains, weakness, and fatigue. Two days before admission he had suddenly been seized with severe, constant, non-radiating substernal pain. There was also moderate dyspnea but no cough, expectoration, or hemoptysis. He offered

From the Medical Wards, Philadelphia General Hospital, service of Dr. William G. Leaman.
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no other complaints except slight burning on urination. He had had an acute urethritis at the age of 17 years and this was presumed to be responsible for the urethral stricture causing urinary retention. He denied any heart disease. The remainder of the interrogation was noncontributory.

Physical Examination.—He appeared dyspneic and critically ill with a temperature of 103° F., pulse rate of 120 per minute respiratory rate of 32, and blood pressure of 110/80. There was slight pallor but no cyanosis or icterus. All superficial lymph nodes were readily palpable; the individual nodes were discrete and moderately tender, and they varied in size from that of a pea to that of a walnut. The spleen was not felt.

The heart was enlarged to the left, approximately 3 cm. beyond the midclavicular line. A systolic and diastolic thrill was palpated, and a rough pericardial friction rub was audible over most of the precordium. The rhythm was regular, the lungs were clear, and the cervical veins were only slightly distended. The liver edge was slightly tender and palpable 1 fingerbreadth beneath the costal margin. A pulsus paradoxus was not obtained; neither was Ewart's sign present.

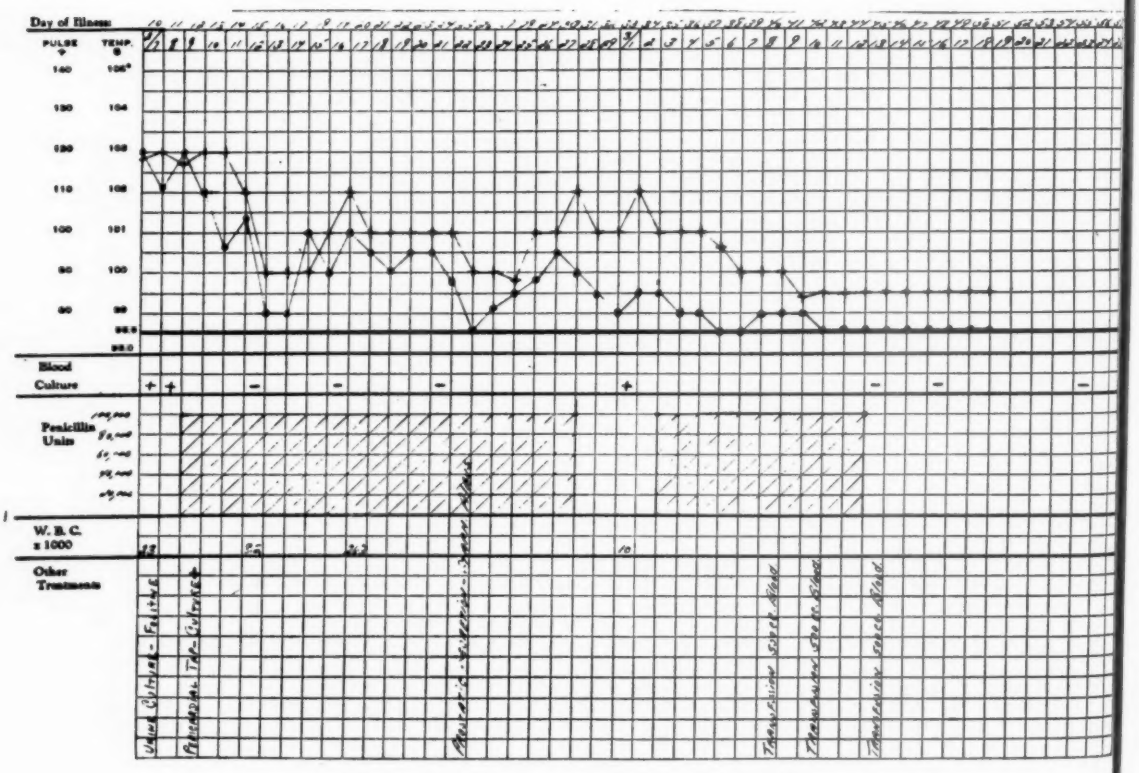
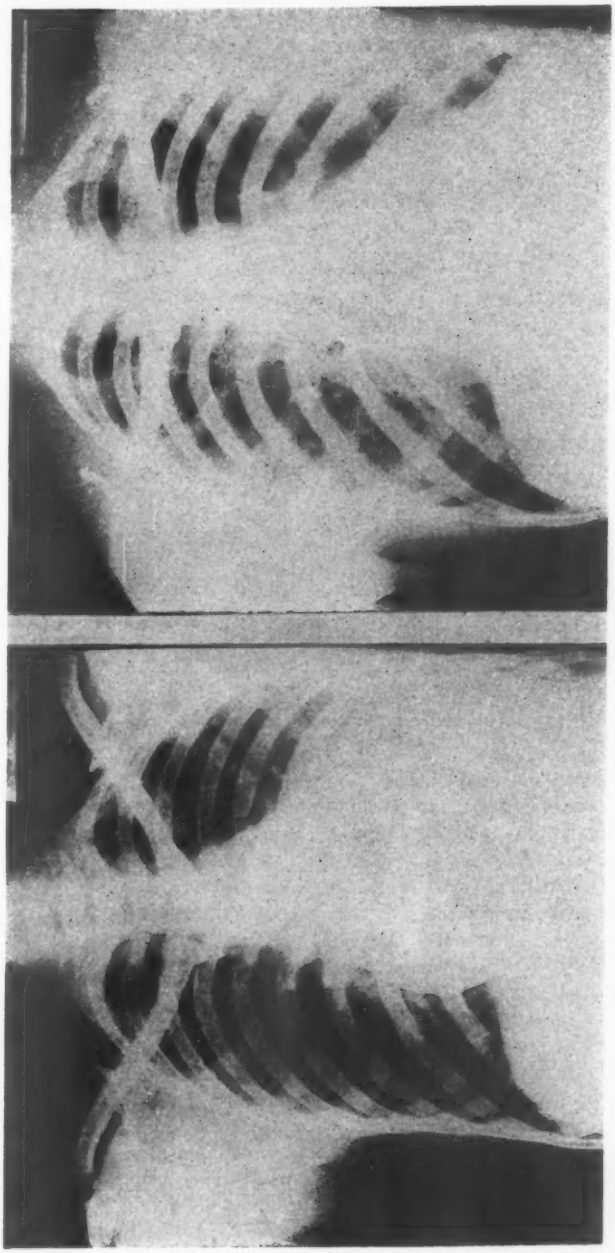


Fig. 1.—Patient's course while in the hospital.

Laboratory Examinations.—Blood: Hemoglobin, 14 Gm.; leucocyte count 23,500 per cubic millimeter; polymorphonuclears, 90 per cent; lymphocytes, 8 per cent; monocytes, 2 per cent. A blood culture was positive for *Staphylococcus aureus.* The blood urea nitrogen was 19 mg. per cent. Kline test was negative. Urinalysis showed: albumin, 1 plus; leucocytes, 3 plus with clumps. Culture of the urine contained *Staph. aureus.* An electrocardiogram revealed the characteristic pattern of acute pericarditis. The findings in an x-ray film of the chest strongly suggested pericardial effusion.

Course.—The administration of sulfadiazine in full doses, instituted immediately after admission, was continued for thirty-six hours with no clinical improvement; 12 Gm. of the drug were given. On February 9, two successive blood cultures (taken on the seventh and eighth) and culture of the urine (taken the eighth) were reported as positive for *Staph. aureus*. The same day pericardial paracentesis was performed and 15 c.c. of straw-colored cloudy fluid were aspirated from the pericardium. At the same time, 10,000 units of penicillin in 10 c.c. of solution were instilled in the pericardial sac through a 21-gauge needle. A culture



A. *B.*

Fig. 2.—*A*, The heart shadow is enlarged. The base of the heart is widened and squared. The cardiac borders are sharply outlined and the left border is straightened. *B*, The heart is slightly enlarged. The contours are normal. The cardiac borders are now normally demonstrated as is the aortic arch.

of the pericardial fluid later revealed *Staph. aureus*. The administration of penicillin was also started intravenously on February 9; 100,000 units were given in 3,000 c.c. of solution per twenty-four hours (2,000 c.c. of 5 per cent glucose and 1,000 c.c. of isotonic saline). After five days, the appearance of thrombophlebitis necessitated the use of the intramuscular route, and the patient received 3 c.c. of diluted penicillin (12,500 units) every three hours, day and night, into alternate sites, from February 14 until the end of treatment.

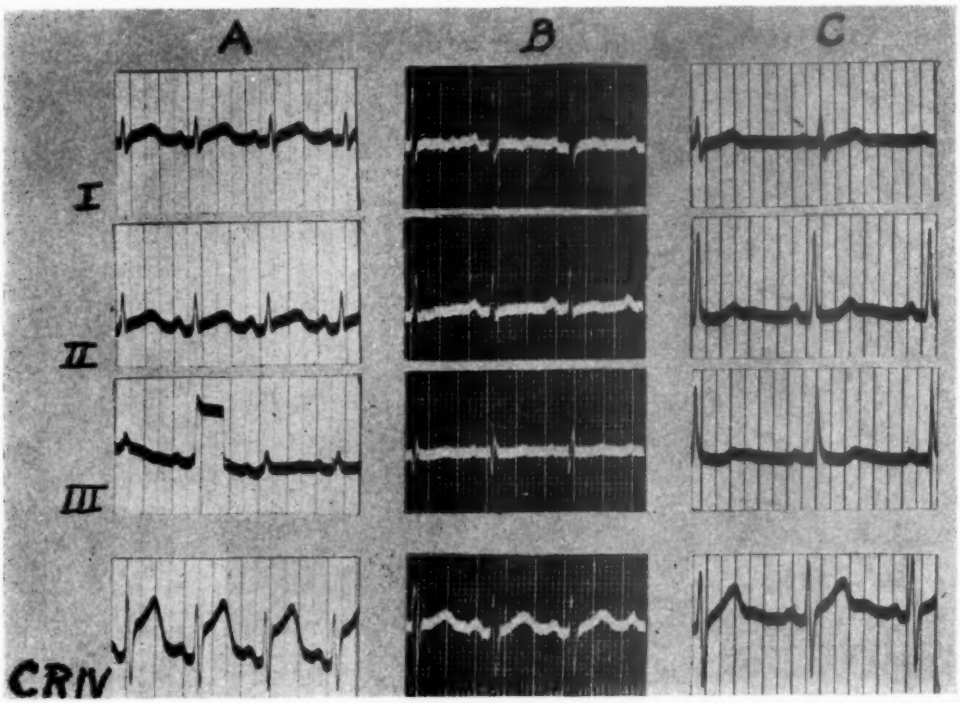


Fig. 3.—*A*, The S-T segments are elevated in Leads I, II, and in the chest lead (*CRIV*). *B*, The S-T segments are no longer elevated; the T waves are inverted in Leads I and II. *C*, This tracing is within normal limits.

Definite clinical improvement became evident on February 12. However, on February 14 an apical systolic murmur was heard for the first time. On February 25 the pericardial friction rub was no longer audible. Although the apical systolic murmur and the fever persisted, it was thought desirable to discontinue penicillin on February 28 since numerous blood cultures had been negative. A blood culture taken March 1, however, was again reported positive for *Staph. aureus*, and penicillin therapy was reinstituted on March 3. The patient was again given 12,500 units intramuscularly every three hours. On March 11, the patient complained of severe generalized pruritus which disappeared promptly when the penicillin was discontinued. At that time the temperature was not yet continuously normal, the apical systolic murmur persisted, and endocarditis was suspected.

The subsequent course proved uneventful, and he was finally discharged March 25, 1944. His progress, both in the hospital and in the cardiac clinic after discharge, may be followed in the accompanying chart (Fig. 1) and by serial roentgenograms (Fig. 2) and electrocardiograms (Fig. 3). The temperature has remained normal, the cardiac silhouette is much smaller, the electrocardiogram has returned to normal, and blood cultures remain negative. The systolic apical murmur persists although it has diminished in intensity. He is again employed in a shipyard, has gained weight, and appears completely recovered, four months after discharge.

DISCUSSION

Although the probable source of the infection was the urinary tract, we have no definite way of establishing this. The patient came to the hospital ten days after urethral instrumentation; most instances of staphylococcus septicemia prove fatal ten to fourteen days after onset of the infection. The electrocardiogram and x-ray studies aided materially in suggesting the localization of the infection in the pericardium, but this could only be positively established by pericardicentesis and the culture of the pericardial fluid.

The administration of penicillin was started intravenously but the development of thrombophlebitis forced the abandonment of this route. There seemed no difference in therapeutic efficacy between the two routes. We have encountered generalized pruritus in other patients receiving penicillin and, as in this instance, the itching disappeared promptly upon discontinuation of the drug. If it is necessary to give the patient more penicillin, simply altering the brand usually prevents recurrence of the pruritus.

We have heard of no cases in which penicillin was used intrapericardially, but this seemed logical.* The procedure did not prove difficult and was apparently without toxic effect. We introduced 10,000 units in 10 c.c. of normal saline solution into the pericardium. There seemed no clinical reason for repetition of this procedure. However, other instances of suppurative pericarditis might very well require repeated tapping and many instillations of penicillin, while still another group[6] may respond to simple intravenous or intramuscular therapy. The regimen in each instance must obviously depend upon the duration and severity of the infection, as well as the type of organism.

CONCLUSIONS

1. A case of proved staphylococcus septicemia which localized in the pericardium is reported. Treatment with sulfadiazine effected no response.

2. Penicillin was used intramuscularly, intravenously, and intrapericardially and in our opinion was responsible for cure of the infection.

We are indebted to Drs. Thomas M. McMillan, Samuel Bellet, and Harrison F. Flippin for criticism and guidance.

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*Since this article was written, reports of several instances of intrapericardial injections with penicillin have come to the author's attention (Hageman, P. O., Martin, S. P., and Wood, W. B.: Pencillin, a Clinical Study of Its Therapeutic Effectiveness, Proc. Central Soc. Clin. Research 16: 18, 1943; and Wise, A. W., and Shafer, L. E.: Purulent Pericardial Effusion Treated With Penicillin Given Intrapericardially, J. A. M. A. 127: 583, 1945).

ELECTROCARDIOGRAPHIC CHANGES RESULTING FROM PHOSPHORUS POISONING

Report of a Case

Lieutenant Colonel Richard A. Dathe, M.C., and
Major David A. Nathan, M.C.

THERE are no reports appearing in the American literature describing the electrocardiographic changes due to phosphorus toxicity. The alteration of the patterns as a result of other exogenous agents and those due to disease are well known. Aberration of one or more of the component waves and prolongation of the P-R interval and Q-T duration have been described. There is no pathognomonic electrocardiographic pattern due to toxic changes in the myocardium, although inversion of the T waves without S-T deviation is the commonest abnormality noted. The T wave in one or more leads may even be coved to simulate a coronary T wave.

An opportunity to study the toxic effect of phosphorus ingestion on the myocardium, as represented in the electrocardiogram, presented itself in a patient who subsequently recovered.

REPORT OF CASE

History.—A 31-year-old white man was admitted to the medical service on Aug. 3, 1943. At 10:00 A.M. the patient swallowed ten large capsules of "rat poison," containing 2½ per cent elemental phosphorus, obtained at a near-by drugstore. A gastric lavage employing potassium permanganate and alkalies was done thirty minutes after ingestion. The lavage returns and subsequent vomitus contained large amounts of smoky phosphorus-smelling material. Four hours later the patient vomited a hemorrhagic tissue identified as gastric mucosa.

Physical Examination.—The patient was acutely ill, the pupils were moderately dilated but equal and reacted to light and accommodation. The conjunctivae were injected. The mucous membranes of the mouth and pharynx were edematous and pale. The heart showed no abnormalities. The rate was 96 per minute, and the blood pressure was 120/85. There was generalized abdominal tenderness to light palpation. No muscle spasm was present. The remainder of the physical examination was noncontributory.

Progress Notes.—During the first five days the patient was very lethargic, although he responded to questioning. Vomiting followed immediately after taking fluids or soft foods. The day after admission the blood pressure dropped to 70/20. The skin was cold and clammy, and the pulse was thready. The heart rate varied from 120 to 140 per minute. The daily blood pressure measurements thereafter were 80/50, 92/60, 100/65, and 106/72. On August 9, i.e., the sixth hospital day, the blood pressure was 120/80. The heart rate decreased as the blood pressure rose. On August 8, edema of the hands and face and oliguria developed. The total daily output of urine varied from 200 to 300 cubic centimeters. Within three days the edema subsided, and the daily urinary excretion was 2,000 cubic centimeters. The specific gravity was 1.008. There were a few hyaline and granular casts and a 1 plus albumin. The highest nonprotein nitrogen level in the blood was 70 mg. per cent, and the

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highest blood creatinine was 2.7 mg. per cent. On the seventh hospital day the temperature rose to 101° F. for the first time and remained between 100 and 101° F. for four days. Two days after the onset of the fever, a generalized scarlatiniform rash developed, followed by a powdery desquamation within twenty-four hours. This was considered to be a toxic dermatitis. The rash disappeared within three days.

Other Laboratory Data.—The lowest red blood cell count was 4,200,000 per cubic millimeter with 85 per cent hemoglobin. The white blood cell count was 15,000 per cubic millimeter on admission and 25,000 three days later. The sedimentation rate on admission was 24 mm. in one hour by the Cutler method. The prothrombin time three days after admission was ten minutes as compared with the normal control of five minutes.

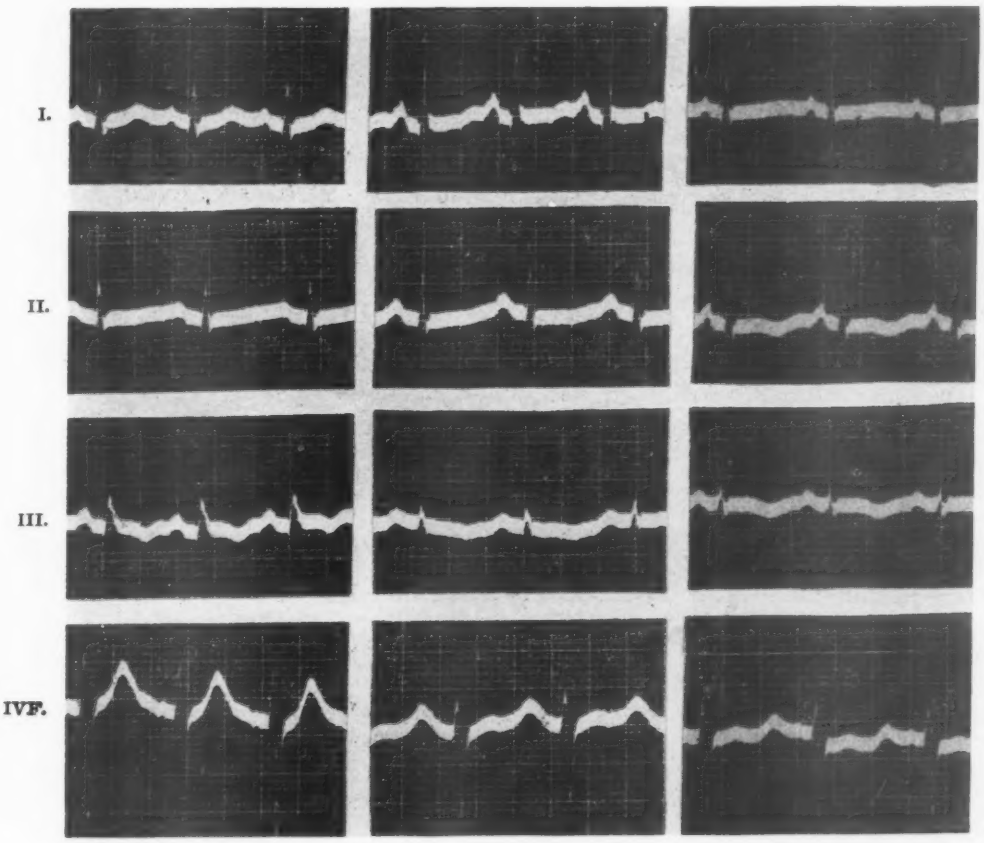

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Aug. 3, 1944, four hours after ingestion of phosphorus; flat T_2, inverted T_3.

Fig. 2.—Aug. 4, 1944, twenty hours later; small T_1 precedes P_1, T_2 not discernible, T_4 decreased in height, and Q-T duration 0.56 second.

Fig. 3.—Aug. 6, 1944; T_1 isoelectric, T_2 inverted, further decrease in height of T_4, and Q-T duration 0.52 second.

Roentgenographic and Electrocardiographic Examination.—Fluoroscopic examination of the heart on the third, seventh, and fifteenth hospital days showed no demonstrable enlargement of the cardiac shadow. Four hours after admission to the hospital, the first electrocardiogram (Fig. 1) was taken. It revealed a sinus tachycardia with a rate of 135 per minute and flat T_2 and inverted T_3 waves. The descending limb of the R_3 deflection was

slurred. The second electrocardiogram (Fig. 2) was taken about twenty hours later. The rate was 108. Small T_1 waves preceded the P_1 deflection. T_2 waves were not discernible; the T_4 deflections were decreased in height; and the Q-T duration was prolonged to 0.56 second. In the third electrocardiogram taken two days later, the rate was 115 per minute. The T_1 waves were unchanged, but the T_2 waves became inverted. There was a further decrease in the height of the T_4 waves, and the Q-T duration was 0.52 second. The fourth electrocardiogram (Fig. 4), taken two days after Fig. 3, showed coving of the S-T segment in Leads I, II, and IV. The Q-T duration was then 0.36 second. The rate was 106 per minute. The T_1 and T_2 waves were inverted, and the T_4 wave was markedly inverted. Subsequent electrocardiograms showed a return of the T waves to the upright position. The inverted T_2 waves noted in Fig. 6 were considered normal in this person.

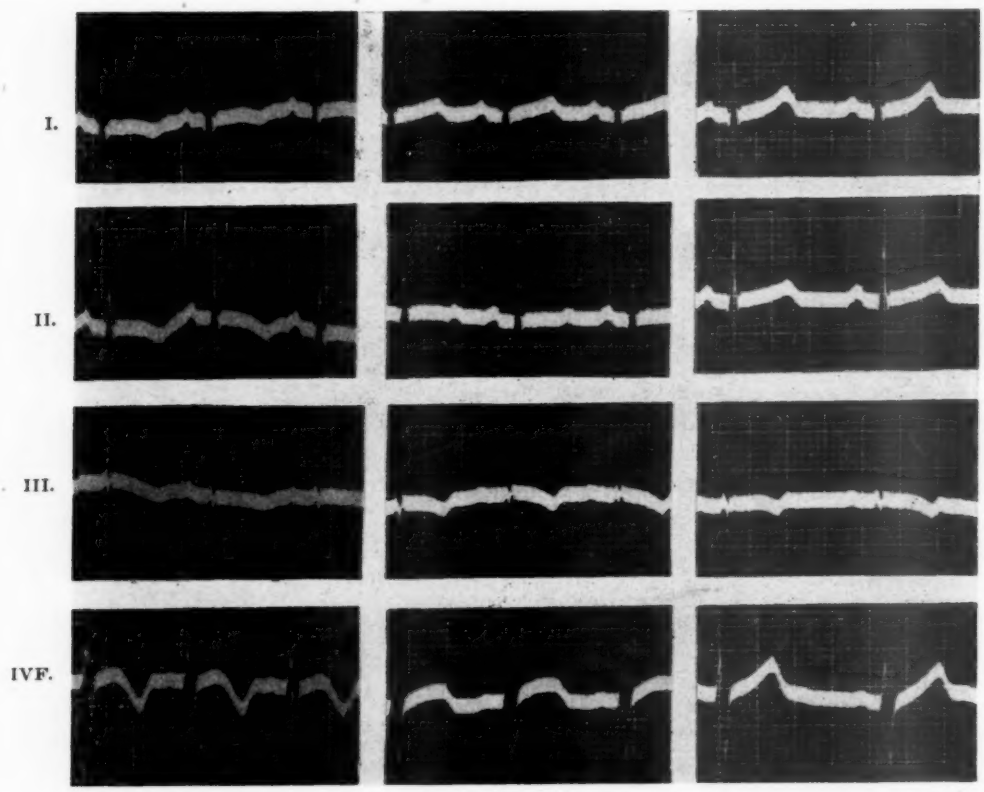

Fig. 4. Fig. 5. Fig. 6.

Fig. 4.—Aug. 9, 1944; note coved S-T_1, S-T_2, and S-T_4; T_1, T_2, and T_4 inverted; Q-T duration 0.36 second.

Fig. 5.—Aug. 16, 1944; return to T_1, T_2, and T_4 to positivity.

Fig. 6.—Aug. 21, 1944; normal electrocardiogram.

COMMENT

The pathologic changes in the viscera due to phosphorus poisoning have been adequately described in the literature. These changes are characterized by fatty infiltration in the liver, central nervous system, kidneys, spleen, and heart. According to Gibbs (quoted by Brescia and Dobbins[1]), phosphorus

causes violent metabolic changes in the cells, leading to a condition not unlike autolysis, and the process is associated with a redistribution of fat from one area to another. Continuation of this process leads to failure of function due to fatty changes. Rabinowitch[2] reports that, after two days, a high degree of "fatty infiltration" develops in the soft organs and heart muscle. Similar reports have been made by Wells,[3] Wertham,[4] and Oliver.[5] There is general agreement that the blood vessels show fatty infiltrative changes as well.

The mechanism responsible for the changes in the electrocardiogram induced by toxic drugs is not understood at the present time. There is a wide range of individual variation in response. The effect of the drug varies with the dosage employed and the duration of medication when the effect is cumulative. Those drugs having an acute action are most likely to produce changes. Katz[6] states that the changes may result from the development of a secondary ischemia of the heart or from stimulation of the cardiac nerve, or they may be the result of direct action on the nodal and conducting tissues causing early evidence of local alteration of conduction. In a few records obtained during acute nephritis, Katz[6] showed changes which resemble the T stage of the anterior wall type of coronary insufficiency. Master and Dack[7] presented twenty-four cases of acute glomerulonephritis, the majority of which showed a coved plane inversion of the T_1 wave and inversion of the T_2 and T_4 waves without S-T segment changes. They postulated that a diffuse arteriolar vascular damage was responsible for these changes. The presence of heart failure was not a factor influencing the electrocardiogram. Aside from drugs, it must be emphasized that tobacco, which appears to be a coronary constrictor, may be the cause of electrocardiographic changes, particularly in susceptible individuals after smoking. White[8] described the case of a healthy young man in whom inhalation of tobacco smoke temporarily produced an inversion of the T waves in Leads I and II so that they resembled, for a few beats, the T waves of coronary disease. Anemia may show similar changes as indicated by Graybiel and White[9] in their text, in which is recorded deeply inverted T waves in Leads I and IV in a patient with a count of 650,000 red blood cells per cubic millimeter. These abnormal components and their coved S-T segments resembled the findings in coronary disease.

The similarity of the afore-mentioned cases and ours is striking. The first changes were noted four hours after phosphorus ingestion. It is evident that one factor, or any combination of factors, may play a role in producing changes in the electrocardiogram in phosphorus poisoning. There may be a diffuse arteriolar vascular damage with a direct effect on the involved coronary arteriolar system or involvement of the heart secondary to kidney damage. Constriction of the coronary vessels and alterations in the carbon dioxide-oxygen exchange may also play a part.

SUMMARY

1. A case of phosphorus poisoning with subsequent recovery is presented to illustrate electrocardiographic findings resulting from toxicity.

2. The electrocardiogram shows progressive and regressive changes in the T waves and S-T segments in L_1, L_2, and L_4.

3. This pattern closely simulates the more frequent changes seen in acute glomerulonephritis, after nicotine inhalation in certain individuals, and in severe anemia.

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CONGENITAL DEFECT OF THE AORTIC VESTIBULE COMPLICATED BY BACTERIAL ENDOCARDITIS WITH PERFORATION AND DEATH FROM CARDIAC TAMPONADE

Report of a Case

Colonel Leon S. Medalia, M.C., and
Major John F. Drapiewski, M.C., Army of the United States

THE case to be reported represents an unusual cardiac anomaly of the aortic vestibule complicated by bacterial endocarditis, which culminated in massive hemopericardium and death from cardiac tamponade. A similar anomaly was not included in Szypulski's[1] series of 124 congenital cardiac defects gathered from 7,500 consecutive autopsies performed at the Philadelphia General Hospital. Rammels and Probst[2] have not described a comparable defect in their collection of 36 cases of congenital heart disease culled from 4,255 autopsies at the University of Pennsylvania Hospital. Abbott[3] in her detailed classification of congenital cardiac anomalies does not refer to a similar case.

REPORT OF CASE

Clinical Abstract.—The patient, a 37-year-old white man, was admitted to the hospital on July 4, 1943. Seven hours previously he had been awakened from his sleep by severe substernal pain, pain in the back of the neck, and dyspnea; there was no radiation of the pain to the shoulders or upper extremities. Although he had had episodes of mild substernal pain at approximately monthly intervals for two years, the present attack was the first of its kind. Physical examination revealed a critically ill patient in severe pain and moderate respiratory distress. The heart was not enlarged to percussion. The cardiac sounds were regular and of good quality but somewhat distant. No murmurs were heard. There were signs of congestion at the base of the right lung. The temperature was normal. The leucocyte count was 15,270 per cubic millimeter, and a urinalysis was negative. One-half grain of morphine failed to relieve the pain. The following day his pain was much relieved, but he still experienced sensations of pressure across the front of the chest and the back of the neck. An electrocardiogram showed a left axis deviation with elevated S-T segments in Leads I and II and an inverted T_3 wave suggestive of acute myocardial infarction.

The patient's course was characterized by episodes of severe substernal pain with radiation to the left shoulder requiring morphine for relief. He became febrile, the temperature at times reaching 101° F. He developed a soft systolic murmur audible at the apex and base. Repeated electrocardiograms were similar to that taken on the day following admission to the hospital. Various laboratory tests were essentially negative, except for a sedimentation rate (Wintrobe) of 26 mm. in one hour. On July 10 a pericardial friction rub was heard. On August 2, a roentgenogram of the chest revealed a wide mediastinal shadow and a pleural effusion on the right. He died suddenly on Aug. 5, 1943, thirty-three days following admission to the hospital.

Clinical Diagnosis.—Acute myocardial infarction and acute fibrinous pericarditis.

Autopsy.—The principal lesions centered about the heart. The parietal pericardium was bulging and fluctuant. When it was incised, approximately 300 c.c. of liquid blood and

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currant jelly clot were evacuated from the pericardial cavity. The parietal pericardium averaged 3 mm. in thickness. Small masses of fresh blood clot adhered firmly to its roughened, granular internal surface. There were easily separated pericardial adhesions at the base of the heart. The epicardial surface was shaggy with many small adherent masses of fresh blood clot. The myocardium showed no evidence of infarction or rupture.

The ventricles were moderately dilated. The mitral, tricuspid, and pulmonic valves revealed no significant abnormality. There was a bicuspid aortic valve. Each cusp measured 2.7 cm. in width. The commissures of the valve were slightly widened. The cusps were moderately thickened with smooth, rolled edges. A single coronary orifice arose from the sinus of the posterior cusp. The artery divided immediately into the right and left branches. No coronary occlusion was apparent and only minimal atherosclerosis was present.

Fig. 1.—Defect below the aortic valve. (U. S. Army Medical Museum, Neg. No. 78667.)

In the posterior wall of the aortic vestibule, 4 mm. below the commissure of the aortic valve, there was an oval defect measuring 1 by 1.3 centimeters. The edges of the defect were smooth, round, and glistening. The defect communicated with an extra cardiac cavity posterior to the root of the aorta. There was no communication with the right ventricle, with either auricle, or with the pulmonary artery. The cavity had a smooth lining and a potential capacity of approximately 30 cubic centimeters. An opening from the cavity easily admitted a probe 2 mm. in diameter connected with the pericardial space at a point superior and anterior to the left auricular appendage. The interventricular and interauricular septa were intact. The heart, with a portion of pericardium attached, weighed 770 grams.

The remainder of the post-mortem examination revealed bilateral hydrothorax, chronic passive congestion of the liver and spleen, and healed, calcified tuberculosis of the mesenteric lymph nodes.

Microscopic Examination.—Sections from several quadrants of the infravalvular defect showed extensive fibrosis of the muscular stroma. Many small, newly formed blood vessels and many lymphocytes and plasma cells were distributed throughout the tissue. In several areas microabscesses composed of lymphocytes and plasma cells were seen. The aortic valve revealed similar inflammatory changes combined with areas of suppuration and aggregations of giant histiocytes along the surface of the valve. At the tip of the valve there was a "fibrinoid" change of the collagen and small deposit of calcium. Sections from the widened commissure showed no evidence of inflammation. The wall of the extracardiac cavity was composed of dense connective tissue, organized blood clot, and granulation tissue.

There was no evidence of splenic infarction or of focal embolic glomerulonephritis.

Fig. 2.—Superior aspect of extracardiac cavity incised to show its interior. (U. S. Army Medical Museum, Neg. No. 78668.)

COMMENT

The infravalvular opening bore a superficial resemblance to a typical interventricular defect. However, the pars membranacea septi was intact and there was no communication with the right ventricle. The bicuspid aortic valve, which met the accepted criteria for a congenital origin, combined with an anom-

alous coronary orifice suggests that the defect, in part, at least, was also of congenital origin. In view of the presence of bacterial endocarditis, the possibility exists that the defect might have been primarily inflammatory in origin. MacCallum[4] described the vagaries of bacterial infection of the endocardium and cited an instance of interventricular defect produced by a mycotic aneurysm of the ventricular septum. In our opinion, the most probable explanation of the case here reported is one of congenital thinning of the infravalvular area. The bacterial endocarditis to which the patient was predisposed because of his other congenital cardiac defects extended to this area. Eventually there was perforation and seepage of blood into the postaortic region. With the gradual enlargement of the infravalvular opening a hematocele posterior to the root of the aorta was formed. The hydrodynamics of cardiac flow finally induced rupture of the hematocele at a weakened point with consequent entrance of blood into the pericardial cavity. The thickened pericardium and the organized blood clot adherent to it compels the assumption that there must have been previous seepage of small amounts of blood into the pericardial space. This hypothesis is consistent with the clinical history of several previous attacks of precordial pain.

SUMMARY

An unusual combination of congenital cardiac defects, complicated by bacterial endocarditis is presented. The endocarditis extended from the bicuspid aortic valve to a congenitally thin aortic vestibule. The latter ulcerated and finally perforated with consequent seepage of blood into the postaortic region. The hematocele thus produced ruptured at a weakened point. Massive hemopericardium and death resulted.

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Abstracts and Reviews

Selected Abstracts

Recarte, P., Duomarco, J., and Rimini, R.: Intraabdominal Pressure and the Regulation of Venous Return. Rev. argent. de cardiol. **11**: 359, 1945.

Arterial blood pressure, abdominal pressure, and pressure in the inferior vena cava were recorded in dogs subjected to: (1) compression of the thoracic portion of the inferior vena cava; (2) compression of the pulmonary hilus; (3) bilateral compression of the carotid arteries; (4) injection of adrenalin; (5) injection of acetylcholine.

No changes in abdominal pressure were observed which would be of any assistance to the vascular reactions consecutive to the mentioned experimental conditions.

These results confirm previous experiments which showed that in normal conditions the difference in pressure between the abdominal and thoracic cavities and its variations have no quantitative influence on the venous return through the inferior vena cava.

AUTHORS.

Martin, L.: The Time of Venous Filling, Cardiologia **6**: 303, 1942.

The application of elementary mathematical physical principles to the clinical research into the filling of the veins permits the construction of a bridge in the appraisement of the degree of circulatory insufficiency between the results obtained by this method and those gained by measuring the pulse volume.

Let us assume that the flow volume in the deep veins and the transudation through the capillaries in a short examination period may be neglected. Let us assume further that there is a direct proportionality between the central (i) and local flow volume (j). The formula

$$R = 3 \frac{Mn - \pi o \cdot 1}{j \quad e'}$$

allows, according to the physiologic laws of P. Govaerts ($0.75' < R < 1'$) in most cases, the determination of the measure of the temporal filling of the veins in various pathologic circulation conditions (Graves' disease, circulatory insufficiency, hypertony, hypotony).

AUTHOR.

Czebrinski, E. W., Smith, J. R., Nemec, S. S., and Robb, J. A.: Measurement of Pulmonary Arterial Pressure in Dogs, J. Lab. & Clin. Med. **30**: 849, 1945.

A method is described for the insertion of a soft rubber urethral catheter into the right ventricle and thence into the pulmonary artery of dogs. Pulmonary arterial pressure may be recorded by an optical manometer. The simplicity of the procedure renders it advantageous where such experimentation on the animal is carried out under anesthesia. AUTHOR.

Ramos, J. G., and Rosenblueth, A.: Action of Heat and Cold on the Different Components of the Electrogram of the Cardiac Ventricle, Arch. Inst. cardiol. México **15**: 101, 1945.

The effects of local heating or cooling of the regions of cardiac ventricles in contact with the electrodes were studied in dogs, cats, turtles, and frogs. The responses were recorded through impolarizable leads and a direct-coupled amplifier by means of a cathode-ray oscillograph. The heating or cooling was achieved by adding a few drops of hot or cold Ringer solution to the moist cotton wicks placed in contact with the tissue and leading to the silver-chlorided needles. The changes recorded were reversible.

In monophasic records heating or cooling the intact recording region resulted in marked changes of the electrogram. Heating or cooling the injured region or other regions including those intermediate to the electrodes had no action.

The changes illustrated cannot be described simply as affecting the amplitude, duration, or shape of the electrogram as a whole. These changes occur selectively and independently in different parts of the records thus indicating that the electrograms are composed of different independent waves. Following the systematization proposed by Rosenblueth, Daughaday, and Bond (1943), summarizes the results observed on the seven components of the electrograms.

As may be seen in the table, the effects of cold are generally, but not invariably, opposite to those of heat. In the four species studied, the effects are generally, but not invariably, similar. The similarity suggests that the different processes which take place in the heart muscle and are revealed by the several components of the electrogram are common to relatively distant species.

The effects of heating or cooling either of the recording regions in diphasic records confirm the view that these records are equivalent to the algebraic sum of two monophasic electrograms.

The present data support the following conclusions, reached in previous studies. When two leads are applied to a tissue the records denote mainly or exclusively the electric variations which take place immediately beneath the leads. There are no injury potentials in ventricular muscle. Monophasic records are monotopic, i.e., they indicate exclusively the changes of potential at the uninjured recording site. Diphasic records are ditopic, i.e., they are the algebraic sum of two monotopic records. AUTHORS.

Ohnell, R. F.: The Wolff-Parkinson-White Syndrome and Related Problems, Cardiologia 6: 332, 1942.

Some problems concerning the etiology and pathophysiology of the so-called Wolff-Parkinson-White syndrome and related cases, are discussed. AUTHOR.

Carral, R.: Critical Study of Unipolar Derivation, Arch. Inst. cardiol. México 15: 161, 1945.

Some of the experiments performed by Wolferth and his collaborators were repeated with the following results. The distribution of the patterns C_1 and C_5 does not always occur in the manner described by the authors cited. Although usually the potential recorded in C_1 is transmitted to the right arm and to the corresponding hemithorax, the potentials recorded from various points in that region are a mixture of those which correspond to the anterior surface of the right ventricle (that which preponderates in C_1 and B′), of the dorsal and lateral aspects of the same ventricle and of the cardiac cavities (the latter predominates in VR and B″ and in the acromion).

The morphologic changes corresponding to tracings obtained by the exploration of several points of the line C_1-right acromion are obvious when the records are made with a central terminal and are less apparent when the Wolferth method of recording is employed. These modifications do not depend on a specific potential of the central terminal that could influence the record; they are the result of the fact that the solid angle comprised is different for each one of the positions studied.

Since the central terminal readily reveals changes which do not appear with an indifferent scapular electrode, it is clear that the first of these two methods of recording gives more accurate results than the second. AUTHOR.

Novelo, S.: The Pulmonary P Wave. Comparative Study of the P Wave in Chronic Mitral and Pulmonary Disease, Arch. Inst. cardiol. México 15: 179, 1945.

An attempt is made to calculate the area of the P wave. Normal means values are Ap 1, 2.2 mv.; Ap 2, 5.0 mv.; and Ap 3, 3.3 mv. The manifest axis of the normal P wave lies at +64°. In all of the cases of pulmonary heart studied, there was a shift of this manifest axis to the right of +64° and in cases of mitral lesions, there was a shift to the left of +64°. The study of the potentials of the limbs showed: (a) that in fourteen cases of

pulmonary heart the area of P on VL was negative: (b) that in all cases of mitral lesion studied the area of P in VL was positive.

It is suggested that the hipertrophy of the left auricle is the cause of the deviation of the manifest axis to the left which is found in the mitral patient and that his auricle transmits its electric potential to VL.

It is also suggested that the dilatation, and in some cases the hipertrophy of the right auricle, is the cause of the deviation of the manifest axis to the right, found in the pulmonary patients, and that this auricle transmits its predominant electric potential to VF.

The pulmonary P wave is considered an excellent sign of the diagnosis of pulmonary hypertension. AUTHOR.

Dustin, P., and Lambert, P. P.: Concerning a Case of Tetralogy of Fallot, Cardiologia 6: 251, 1942.

The case history is given of a 16-year-old patient with a congenital heart trouble with severe cyanosis, dyspnea and hippocratism of the nails. Death occurred after repeated profuse hemoptysis, so that there was a Fallot's tetralogy, characterized by a very definite pulmonary stenosis with total dextroposition of the aorta.

The malformations revealed peculiarities rarely observed, especially in adults. The stenosis of the pulmonary artery was so pronounced, that on first examination it was thought to be a case of total aplasia (tronc arteriel unique). The structure of the canalis in fundibularis, deeply situated in the myocardium of the right ventricle, was from the phylogenetic point of view very interesting. Its upper boundary was formed by two small sigmoidal valves, which showed no endocarditic changes. On the other hand, the lower opening of this canal (ostium infundibuli) showed a fibrous narrowing on to which, a florid endocarditis had been formed. The authors have shown how these pecularities are to be explained, when with Keith it is assumed that the canalis infundibularis corresponds to the conus arteriosus of the lower vertebrates. In this case, the embodying of the latter in the ventricle was very incomplete.

The authors have pointed out that the structure of the bentricle, which was otherwise absolutely normal (when one, according to Spitzer's phylogenetic theory, leaves the interventricular connection out of consideration) was difficult to value.

The very rare localization of the inflammatory alterations approach the form described by Bedford and Brown. In their case, however, pulmonary stenosis was confined to the lower opening of the infundibulum ("lower bulbar stenosis").

In this patient, the endocarditis caused thrombosis of the pulmonary artery and its branches, causing a massive and fatal infarction of the left lung. This development (along with the anatomic observations) shows that, in spite of the long survival with every considerable pulmonary stenosis, in the patient no substantial bronchial collateral circulation had been formed. If such patients live long enough, strongly dilated bronchial vessels are usually seen (East and Barnard).

The most interesting pecularities of this case are briefly: the long life in spite of the considerable pulmonary atresia and the absence of a compensatory collateral circulation; the structure of the canalis infundibularis; the site of the endocarditic alterations and the terminal, massive, fatal infarction of an entire lung. AUTHORS.

Butt, H. R., Leake, W. H., Solley, R. F., Griffith, G. C., Huntington, R. W., and Montgomery, H.: Studies in Rheumatic Fever, J. A. M. A. 128: 1195, 1945.

From this study the following observations were made:

The administration of sodium salicylate with sodium bicarbonate in therapeutic doses to patients with rheumatic fever is followed by an increase in the Quick prothrombin time. In none of the cases reported were any hemorrhagic manifestations noted following the administration of salicylates.

Under the circumstances of this study, the administration of salicylates had no deleterious effect on the hepatic parenchyma.

A dosage of 150 grains (10 Gm.) of sodium salicylate daily is followed in most instances by a blood level of salicylate of 30 to 50 mg. per hundred cubic centimeters. When the level of salicylates in the blood falls much below these figures, one can suspect that the patient is not taking the drug.

In recurrent attacks of polycyclic rheumatic fever the sedimentation rate is little affected by the administration of salicylates.

Long-continued, high dosage of salicylates is followed by a slight reduction in the hemoglobin content and erythrocyte count. The leucocyte count is unaffected by salicylates, as is the urine. AUTHORS.

Bing, R. J., Thomas, C. B., and Waples, E. C.: The Circulation in Experimental Neurogenic Hypertension, J. Clin. Investigation 24: 513, 1945.

The hemodynamic alterations during chronic neurogenic hypertension were studied in six unanesthetized dogs.

Following the establishment of hypertension, the cardiac output rose, while the difference in the oxygen content between arterial and mixed venous blood, and the coefficient of oxygen utilization decreased. Since the heart rate increased, the systolic discharge and the right auricular pressure remained at their prehypertensive levels. The total resistance showed no change in four dogs, while it rose in the remainder of the animals.

The blood flow through the kidney and the glomerual filtration rate fell in two animals and remained constant in the rest. The decline in the renal fraction and the rise in the renal vascular resistance are evidenced of renal arteriolar constriction. This takes place presumably in the afferent arterioles as the filtrate fraction remained constant.

The development of neurogenic hypertension was followed by a marked rise in the blood flow through the forelimb and a fall of the vascular resistance through the extremity.

The changes described in this paper are compatible with increased sympathetic tone

Differences in the vascular dynamics between neurogenic hypertension, experimental renal hypertension, and essential hypertension, are discussed. AUTHORS

Harvey, R. A.: Nodules in Rheumatic Fever. Arch. Pediat. 62: 302, 1945.

This clinico-pathologic study, made by a student in the junior class of Western Reserve University as a part of the requirements of the Pediatrics Department, gives a good summary of our knowledge of the clinical manifestations and the causes of subcutaneous and Aschoff's nodules in rheumatic fever.

Johnson, John J.: Some Experimental Aspects of Streptococcus Infection and Rheumatic Fever. Arch. Pediat. 62: 387, 1945.

In 1944 the author was able to produce a picture quite closely resembling human carditis by injecting bacteria-free filtrates of a virulent streptococcus. Working with the same organism a year later, he was unable to reproduce these lesions. He was also unable to reproduce the picture of rheumatic carditis by injecting horse serum as Rich and Gregory did. However, if he first gave horse serum intravenously to rabbits and then, twelve to twenty days later, introduced a sterile streptococcic filtrate, at least a mild carditis resulted. The author concludes, therefore, that horse serum, which alone did not produce carditis, did injure the hearts in such a way that they became more susceptible to injury from a bacteria-free streptococcic filtrate.

Trent, Josiah C.: Surgical Therapy of the Patent Ductus Arteriosus. Arch Surg. 51: 106, 1945.

This report adds five more to the growing list of patients successfully operated on for this congenital lesion. One of the five patients had proved bacterial endocarditis and has remained well for two years after operation. Sulfadiazine was used for twelve days postoperatively.

Clawson, B. J.: Experimental Endocarditis, Rheumatic-Like and Bacterial, in Rats. Arch. Path. 40: 153, 1945.

The author concludes that valvular lesions closely simulating acute rheumatic endocarditis anatomically can be produced in a high percentage of rats by injecting either *Streptococcus viridans* or *Streptococcus haemolyticus* into the blood stream.

Lesions similar to human bacterial endocarditis may occur on the same or separate valves in association with the rheumatic-like vegetations, or the bacterial vegetations may occur separately.

These rheumatic-like and bacterial lesions are produced only when the bacterial organisms are in the blood stream. Endocarditis fails to develop following the injection of other proteins: Dick toxin, rabbit and horse serum, egg albumen, and extract of *Streptococcus viridans.*

Agglutinins in the blood stream apparently favor the development of the valvulitis.

Hypersensitiveness (allergy), immediate (anaphylactic) or delayed (bacterial), does not appear to be a factor in the genesis of the endocarditis except possibly in the bacterial form of endocarditis, in which the delayed type of hypersensitiveness may be an influencing factor.

These experiments support the theory that acute rheumatic endocarditis and bacterial endocarditis are etiologically similar but differ in degree of manifestation and that they occur as a response to a direct valvular infection with the bacterial cells. AUTHOR.

Steinburg, G. LeRoy: Gout and Its Effect on the Cardio-Vascular System. Ann. Rheumat. Dis. 4: 51, 1945.

No evidence was found to indicate that gout was a factor in hypertension. Of 46 patients studied only 14 had hypertension while 32 did not. Moreover, 18 of the 32 patients who had no hypertension had had gout for more than five years.

No evidence was found to indicate that gout predisposed to renal lithiasis. Only one of the 46 patients showed kidney stones and these had been evident seven years before gout showed itself.

No association between gout and angina pectoris was found in this series of patients. Only three of the 46 patients had angina pectoris, and in two of these there was an associated hypertension.

Zimmerman, S. L.: Ventricular Tachycardia—A Report on Ten Cases, Eight of Which Were Treated With Quinidine With Recovery in Seven. Ann. Int. Med. 23: 634, 1945.

Ten cases of ventricular tachycardia are reported and discussed from the standpoint of underlying heart disease, causal effects of digitalis, ventricular rates, QRS intervals and the presence of congestive cardiac failure. Digitalis was not causal in the production of the arrhythmia in any of the reported cases. Five of the ten cases complicated myocardial infarction. In one case no underlying cardiac disease could be demonstrated. In the remaining cases coronary disease, alone or in association with hypertension, was easily established.

Eight of the ten patients were treated with relatively large doses of quinidine. Seven of these patients recovered. Three of these paroxysms complicated myocardial infarctions, and were successfully treated. The only death occurred in a patient who had a massive anterior wall infarction and who appeared in a terminal state even prior to the onset of the arrhythmia.

The total amount of quinidine required to terminate the arrhythmia varied greatly from case to case. Large doses were given unhesitatingly with extremely gratifying results. Toxic signs and symptoms were negligible. The QRS interval was disregarded as an index of quinidine toxicity.

The recent literature bearing on the subject has been discussed. Relatively few reports dealing with the effect of large doses of quinidine on this arrhythmia have been noticed.

From a review of this series, and as a result of the perusal of the sparse recent literature, quinidine in adequate and massive doses, if necessary, is recommended in the treatment of ventricular tachycardia. There does not appear to be any unequivocal evidence that its administration following acute coronary occlusions is in any way detrimental.

AUTHOR.

Candel, Samuel, and Wheelock, M. C.: Acute Non-Specific Myocarditis. Ann. Int. Med. 23: 309, 1945.

Eleven cases of acute myocarditis, nonspecific in nature, have been presented. The studies are entirely clinical. The reasons for the diagnoses are presented. Evidence is shown that myocarditis occurs more frequently than has been supposed. Some of the reasons for failure to recognize the condition are indicated. Acute myocarditis is discussed. The importance of a better understanding and a wider appreciation of acute nonspecific myocarditis is stressed. It is pointed out that failure to appreciate the frequency of myocarditis may affect adversely some of the current research.

A case of acute myocarditis, following acute suppurative tonsillitis and eventuating in death, is described. As far as we know, this is the first case on record (proved by autopsy) of acute nonspecific myocarditis following acute tonsillitis. AUTHORS.

Grollman, A., Harrison, T. R., Mason, M. F., Baxter, J., Crampton, J., and Reichsman, F.: Sodium Restriction in the Diet for Hypertension. J. A. M. A. 129: 533, 1945.

Diets rendered low in sodium content by dialysis were found to reduce decidedly the blood pressure of rats with experimental renal hypertension. That this effect was due to the low sodium content of such diets was demonstrated. It was also shown that prolonged administration of such "low sodium" diets not only was not deleterious but apparently actually prolonged the life of the experimental hypertensive animal.

In six human hypertensive patients a drastic reduction in the sodium intake, made possible by dialysis of the milk included in the diet, resulted in no decline in blood pressure in one subject, a reduction of the pressure to essentially normal levels in two, and a moderate reduction in the remaining three, one of whom, however, displayed acute circulatory collapse which responded promptly to sodium chloride therapy. It is suggested that such diets be utilized for a brief trial period for patients with hypertension and employed for a longer period in subjects who display a favorable response. AUTHORS.

Gross, Robert E., and Hufnagel, C. A.: Coarctation of the Aorta. Experimental Studies Regarding Its Surgical Correction. New England J. Med. 233: 287, 1945.

Previously recommended procedures for the surgical relief of coarctation of the aorta have included anastomosing a subclavian artery into the aorta distal to its obstruction, removing the constriction, and replacing the removed portion of the aorta either by a vein or by a portion of aorta previously secured at necropsy.

After considering these surgical approaches, Gross and Hufnagel felt that it was theoretically possible to remove the constriction and directly reunite the upper and lower portions of the divided aorta end to end. This was tried experimentally on dogs and gave encouraging results.

The three chief difficulties that were encountered were: thrombus formation at the site of suture of the aorta, fatal dilatation of the heart at the time of the removal of the clamps from the aorta, and hind-leg paralysis secondary to ischemia of the spinal cord.

After finding methods of combating these complications, the surgical procedure was applied to two humans. The first patient was a 6-year-old boy who stood the operation satisfactorily until the clamps were removed from the aorta. At this point the heart became enormously dilated and the child died. The second patient was a 12-year-old girl. The clamps in this instance were very gradually released, a full ten minutes being taken to accomplish

complete opening. There were no deleterious effects. The systolic blood pressure in the arms was 215 before operation and 140 after operation. Preoperatively no systolic readings could be obtained in the legs. After operation the systolic pressure in the legs was 145 and pulsations of the femoral artery were readily felt.

Gross, Robert E.: Surgical Relief for Tracheal Obstruction From a Vascular Ring. New England J. Med. **233**: 586, 1945.

A child of 4 months who had had wheezing, difficult respiration since birth and who periodically developed attacks of tracheobronchitis with an increase of dyspnea, cough, and fever was studied by Gross. Both from the literature and from necropsy experience he was aware that occasionally the trachea was obstructed by vascular elements. The obstruction comes about in two ways. A patent ductus arteriosus or a ligamentum arteriosum may make traction on the pulmonary artery, which is, of course, in front of the trachea, and thus compress the trachea sufficiently to produce symptoms. The other form of vascular obstruction of the trachea occurs when the arch of the aorta splits, with one portion going in front of the trachea and the other portion behind the esophagus. In the case described by Gross, obstruction of the trachea was strongly suspected, and indeed diagnosed, in life. The diagnosis was based principally on the fact that lipiodol showed the trachea to be compressed in front, and barium showed the esophagus to be compressed posteriorly. Both forms of obstruction were present. Separation of the ligamentum arteriosum partially relieved the pressure of the pulmonary artery on the trachea. Because the posterior branch of the aorta was the larger, the anterior branch was separated at a point between the left common carotid artery and the left subclavian artery. The results were very satisfactory. So far as the author is aware this is the first time this operation has been performed.

High, R. H., and Aegerter, E. E.: Rheumatic Heart Disease Associated With Meningo Encephalitis. J. Pediat. **27**: 343, 1945.

A Negro boy, aged 12 years, who had first had rheumatic fever at the age of 5, had evidences of severe meningeal irritation. At necropsy there was unmistakable evidence of an active rheumatic carditis. The meninges, brain, and spinal cord showed a marked and rather unusual inflammatory reaction consisting of an abundant lymphocytic infiltration about most of the small vessels. In some areas, mingled with the lymphocytes, were large cells resembling those seen in an Aschoff body. The morphology and pattern were hardly identical with that of an Aschoff nodule, but the cellular elements were the same. The implication is that the changes in the nervous system and the heart were the result of the same etiological factor. BELLET.

Announcement

The American College of Physicians will resume its Annual Meetings in 1946. The meeting will be held in Philadelphia, May 13 to 17, inclusive, under the presidency of Dr. Ernest E. Irons, Chicago, and the general chairmanship of Dr. Morris Piersol, Philadelphia. The headquarters will be at the Philadelphia Municipal Auditorium, 34th Street below Spruce Street.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.